Introduction

Higher resolution, better sensitivity, and excellent reproducibility: this is how Dynamic Image Analysis (DIA) improves the characterization of powders and granulates in both quality control and R&D. This white paper outlines how particle size distribution and particle shape are determined by DIA, illustrated by application examples from the pharmaceutical industry which prove the superiority of the method over sieve analysis and laser diffraction.

Traditional techniques for particle size distribution analysis of pharmaceutical samples are sieve analysis, microscopy or laser diffraction. These methods are established in the pharmacopoeia and are used in pharmaceutical laboratories all over the world.

With the introduction of Dynamic Image Analysis (DIA) as an alternative method, it is now possible to measure particle size and shape of powders, granulates, pellets and suspensions of particles > 1 µm. A number of trials clearly demonstrate the advantages of DIA compared to the traditional particle sizing methods. Many pharmaceutical companies have already recognized the potential of this method and added this technology to their research and quality control labs. Typical application examples are:

- Micronized active ingredients (APIs) and excipients
- Pharmaceutical granulates (e.g. tableting mixtures)
- Size and shape of pellets
- Monitoring of coating processes
- Characterization of crystalline APIs and excipients
The principle of Dynamic Image Analysis (DIA)

Just like microscopes, DIA analyzers consist of an illumination unit, objective lenses and a camera system. Particles are usually detected in transmitted light and the images contain shadow projections of the particles. Unlike microscopy however, the objective of DIA is the detection and evaluation a vast number of particles in a very short analysis time. This is achieved by generating a flow of particles which is photographed by high-speed cameras (Fig. 1). The particle flow can be in free fall for pourable solids, in an air flow generated by a Venturi nozzle for agglomerated powders, or even in a liquid suspension. Depending on the instrument and the application, between 60 and 320 images are acquired and evaluated in real time!

An automated microscope will typically need 30-60 minutes to capture enough particles to calculate a meaningful size distribution. DIA systems evaluate some hundreds of thousands or even millions of particles within a few minutes. The resulting size distribution is therefore based on a much larger basis, eliminating errors arising from sampling and poor statistics. Additionally, the measurement range of a DIA system is more than 10 times larger than that of a microscope – a significant advantage as many samples contain particles from the micron to the millimeter range.

Imaging techniques provide a direct approach to particle size analysis. The basic idea is simple: “What you see is what you get”. Based on pictures of individual particles, automatic software algorithms determine size and morphology. Particle length and particle width are directly accessible, as shown in Fig. 2. This shows the versatility of DIA, particularly in combination with shape analysis which runs simultaneously to the size measurement. Some shape parameters are explained in Fig. 3.
Example 1: Detection of agglomerates during pellet production

The production of pharmaceutical pellets is typically done by granulation, extrusion with subsequent spherization or coating. The desired result is a narrow and homogeneous particle size distribution of round particles. In the granulation and coating processes, the formation of agglomerates is an unwanted side effect. Agglomerates can have a negative impact on product properties; they can lead, for example, to changes in the solubility or the release rate of the active ingredients. Therefore, the amount of agglomerates is usually strictly controlled for each product batch. The CAMSIZER is able to detect percentages of agglomerates as low as 0.05%. Neither laser diffraction nor sieve analysis are suitable methods to reliably detect such minor percentages. Due to the measuring principle laser particle analyzers require a minimum concentration of 2% to detect agglomerates or undersized particles, such as dust fractions. Smaller amounts may be simply ignored by the software. Particle shape is also an important factor in this context. Elongated particles, for example, can neither be detected with laser diffraction nor with sieve analysis.
Example 2: Measuring coating thickness

The various coating steps when producing pellets require precise analysis of the coat thickness of the applied layers. The total dosage of the drug layer is defined by its thickness; the thickness of other functional layers can control the drug release rate and dissolution process. The drug release is inversely proportional to the thickness of the polymer membrane layers, and proportional to the surface area of the particles. With Dynamic Image Analysis it is possible to reliably determine variations in the coating thickness of less than 1 micron. The method combines both high resolution and excellent statistics as a great number of particles is analyzed in a very short time. Sieve analysis, however, only offers low resolution, as typically only very few sieve sizes are available in the narrow size range of coated granules. Traditional microscope-based technologies such as SEM or static light microscopy offer excellent resolution but only for very few particles. [2] [3] [4]

Example 3: Tabletting Mixture

In tableting, the goal is usually to generate a product that has low friability and high tensile strength [5]. By analyzing the size distribution, it is possible to predict the suitability of a mixture for tableting. The starting products are often granulates with a wide size distribution and irregular particle shape. Both properties contribute to the compactability and have an influence on the mechanical properties of the mixture. This is why dynamic image analysis provides valuable information besides particle size to characterize a bulk material and relate these to its mechanical properties. Note that in the example below the DIA result largely matches those of sieve analysis. Hence, it is possible (and advisable) to replace the inaccurate, low resolution and time-consuming sieving method with a faster, more accurate and highly automated technique. This mixture has a size distribution from 10µm to 1.5 mm and the CAMSIZER X2 DIA analyzer is able to determine the entire distribution without any hardware adjustment. Subsequent examination of individual particles gives a thorough understanding of the material at hand.
Example 4: Size and shape analysis of starch

Starch is a common excipient in pharmaceutical applications. It comes from various vegetable sources and in various size ranges. The example shows the results of two different starch samples. The distribution is slightly different but the median (d50) value is almost identical. Considering the particle shape, it becomes very clear that sample 1 consists of round, compact grains whereas sample 2 contains a significant amount of fibres!
A common particle analysis technique is laser diffraction. This method is fast, robust and suitable for routine analysis. Its greatest flaw, however, is the fact that it does not consider the real geometry of the particles but rather relates every measurement signal to the diameter of an equivalent sphere. Thus, it totally neglects particle shape. An additional drawback is that laser diffraction is evaluating a scattering pattern that is simultaneously generated by a collective of particles. Small amounts of oversize and undersize are lost due to the low sensitivity of the method. Fig. 9 shows that the result of laser diffraction analysis correlates with the size definition xarea of the Digital Image Analysis.

Example 5: “Unsievable” APIs

Particle size analysis of micronized APIs can be a nightmare for any lab technician since these powders often show very disadvantageous properties: the material can be sticky, cohesive, charged or highly agglomerated. All this makes an effective sieving process virtually impossible. Furthermore, below 100 µm size resolution and accuracy are limited. Regular vibratory sieving is not applicable here; air-jet sieving is a suitable method but only provides sieve cuts. DIA analyzers like the CAMSIZER X2 provide efficient dispersion systems to handle problematic samples.
The powder is either suspended in a suitable liquid (water, alcohol, non-polar organic solvent or plant oil) or the particles are separated in an air-flow generated by a Venturi-nozzle. The dispersion pressure can be adjusted to achieve efficient separation of particles without any unwanted milling effect.

Fig. 11 Agglomerated API on a 63 µm sieve after 2 minutes of air-jet sieving (photo). Due to its cohesive nature the sample is “unsievable”. With the air-jet dispersion of the CAMSIZER X2 the separation of particles can be achieved. The higher the pressure, the finer the result. Perfect dispersion is established at 200 kPa. CAMSIZER X2 results at 30 kPa (orange), 80 kPa (red), 150 kPa (blue), 200 kPa (brown) and 300 kPa (green).
3. CONCLUSION

Modern DIA analyzers like RETSCH Technology’s CAMSIZER P4 or CAMSIZER X2 are not only capable of replacing traditional particle sizing techniques like sieve analysis or laser diffraction; they also provide a wealth of additional information which the other methods lack. If the correct size definition is selected, the results are virtually identical and product specifications can remain unchanged. Users of DIA benefit from highest reproducibility, improved accuracy and sensitivity as well as from short analysis time and additional shape information.

References:


2. Grant Heinicke and Joseph B. Schwartz, ”Particle Size Distribution of Inert Spheres and Pelletized Pharmaceutical Products by Image”, Pharmaceutical Development and Technology Vol. 9, No. 4, pp. 359-367, 2004

