Retsch TECHNOLOGY
Solutions in Particle Sizing

Particle Characterization with Dynamic Image Analysis

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Seeing is believing: Particle size and shape measurement of powders, granules, pellets and suspensions with Dynamic Image Analysis

Higher resolution, lower detection limit, and better reproducibility: that is what Dynamic Image Analysis offers the next generation of size analysis instruments. This white paper outlines how the method works, and shows application examples from typical granulation processes. Pros and cons compared to established methods, like sieving and laser diffraction, are discussed.

Traditionally, particle size distribution analysis of pharmaceutical powders and granules is carried out by sieve analysis, microscopy or with laser diffraction. These methods are established in the pharmacopoeia and used routinely 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 sizes >1 micron of powders, granules, pellets and suspensions as well as particle shape. A number of trials clearly demonstrate the advantages of DIA compared to the established particle sizing methods. In addition to particle size analysis with very high resolution, image analysis provides important information about the particle shape. Many pharmaceutical companies have already recognized the potential of this method, and added this instrumentation to their research and quality control labs, for example for the analysis of multi-particulate dosage forms.

1. The Principle of Dynamic Image Analysis (DIA)

Dynamic Image Analysis principally works like a microscope: a camera takes enlarged digital pictures of the particles which are then analyzed by a software which calculates the size and form parameters of every single particle. There are two main differences between DIA and conventional microscopy. Conventional microscopy for particle sizing is a static method, i. e. the particles lie on the object plate without moving in relation to the optics. Dynamic Image Analysis, however, captures the pictures of particles in motion. A particle stream is generated either by gravity, air pressure or in a liquid which passes the camera, and pictures are taken of the particles in quick succession.

This leads to the second difference. **With Dynamic Image Analysis it is possible to measure ten thousands of images per minute** whereas static analysis methods base their calculations on a few images only.

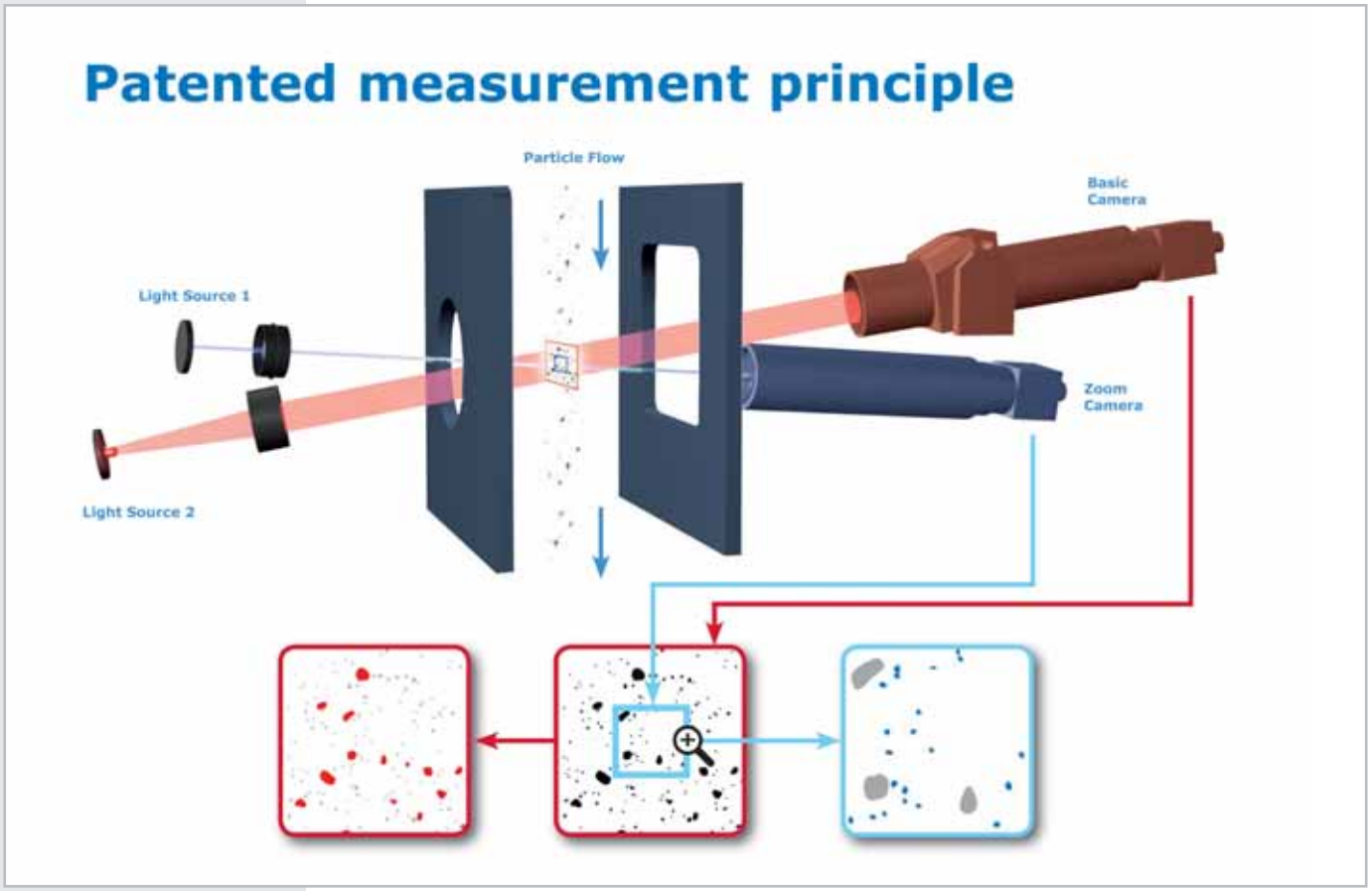

Fig. 1: Measuring Principle Dynamic Image Analysis

Figure 1 shows the principal set-up of the optics for Dynamic Image Analysis. The sample moves as a particle flow through the measuring field. A light source illuminates the particles from one direction while a camera takes their picture from the opposite side. The projections of the particles are evaluated by the software to determine the size distribution of the sample in a very short time. A few hundred particles per picture are evaluated in real time. Advanced DIA systems, such as Retsch Technology's CAMSIZER and CAMSIZER XT use two cameras with different magnifications to cover a wide measuring range: one camera with high magnification is optimized for the analysis of small particles, a second camera with a lower magnification but wide field of view allows to simultaneously analyze the larger particles with high detection efficiency. The CAMSIZER XT system records more than 275 pictures per second. **Thus Dynamic Image Analysis allows for measuring statistically relevant amounts of a few million particles in a short time.** This method provides reproducible results not only for the mean particle size but also for smallest amounts of undersized or oversized particles.

Fig. 2: The CAMSIZER and CAMSIZER XT reliably determine the particle size and particle form in a measuring range from 1 µm to 30 mm

2. Advantages of Dynamic Image Analysis compared to sieve analysis and laser diffraction

DIA is an individual measuring method recording the particle size and shape of every single photographed particle. Laser diffraction and sieve analysis, however, are collective measuring methods; this means that measuring data which are characteristic of the particle size are obtained as superimposed signals from a collective of particles. By directly measuring the individual particle, DIA provides particle size distributions with a considerably higher resolution, and, moreover, adds information about the particle shape.

2.1. Identical results to sieve analysis

A key advantage of DIA-based instruments such as the CAMSIZER is the possibility to obtain particle size distributions which are identical to the results of sieve analysis. This facilitates the replacement of sieve shakers with this faster, more accurate and less time consuming method as no change of product specifications is required.

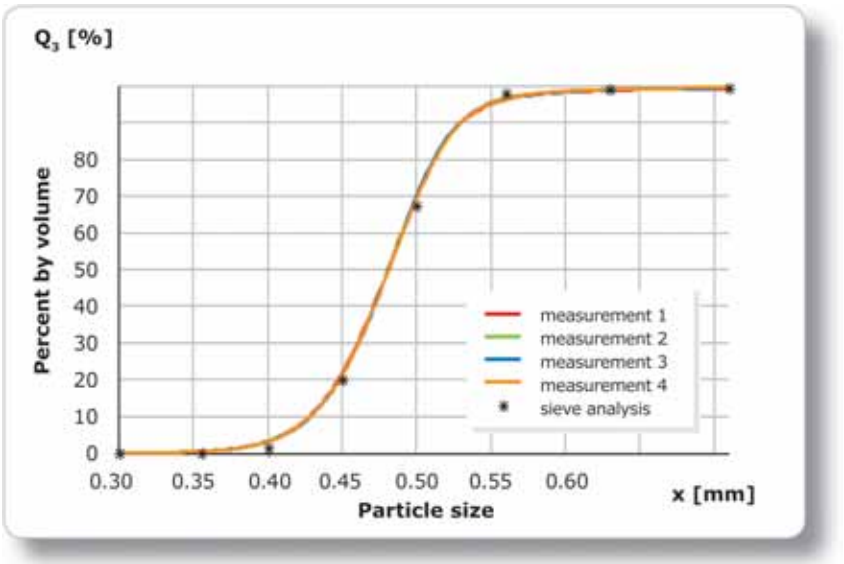

Fig. 3: Comparison of four CAMSIZER measurement results with the results of sieve analysis. The CAMSIZER data perfectly match the sieving results. The four measurements also demonstrate the excellent reproducibility.

2.2. Detection of agglomerates during pellet production

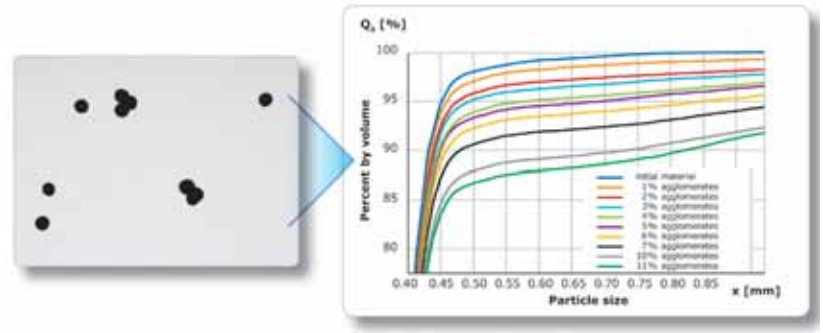

Fig. 4: The graphic shows the reliable detection of oversized agglomerates by the CAMSIZER. Approx. 0.21 g of agglomerates, which is equal to about 10 particles, have been repeatedly added to a sample of 21 g to achieve mixtures in the range of 1 % to 11 %. The percentage of oversized particles at 0.7 mm exactly matches the calculated mixing percentages.

The production of pharmaceutical pellets is typically done by granulation, extrusion with subsequent spheronization 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.

2.3. Measurement of coating thickness

The various coating steps when producing heterogeneous 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. [1] [2] [3]

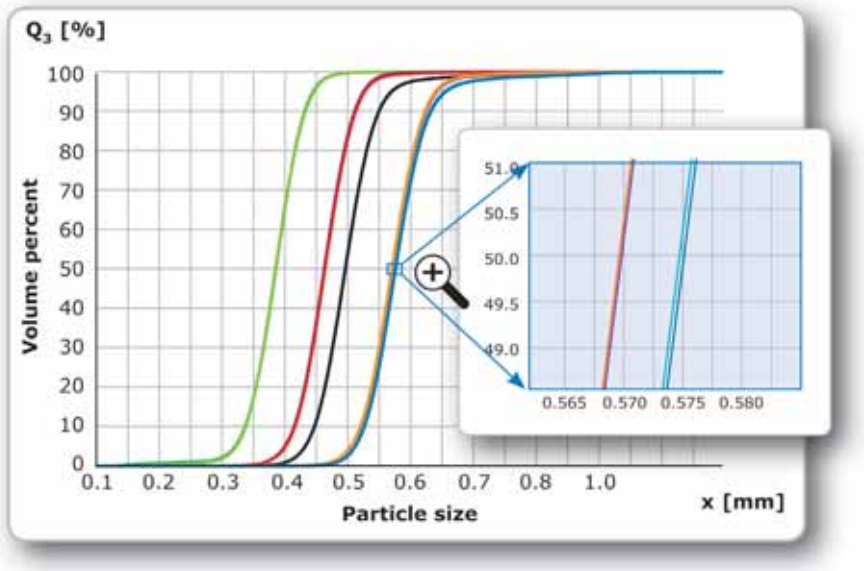

Fig. 5: Particle size distributions after different process steps during coating, ranging from the small nonpareil starting pellets to the final product after polymer coating. The detection of smallest changes in the average particle diameter allow the precise measurement of the coating thickness. The width of the size distributions enables a characterization of the homogeneity of the coating process.

Dynamic Image Analysis allows for simultaneous characterization of particle size and shape in one analysis. The "roundness" or "elongation" as well as the "surface roughness" can be compared for different stages of the layering process. Fig. 6 shows that the nonpareil starting pellets originally had a more elongated form, which became rounder during subsequent processing steps.

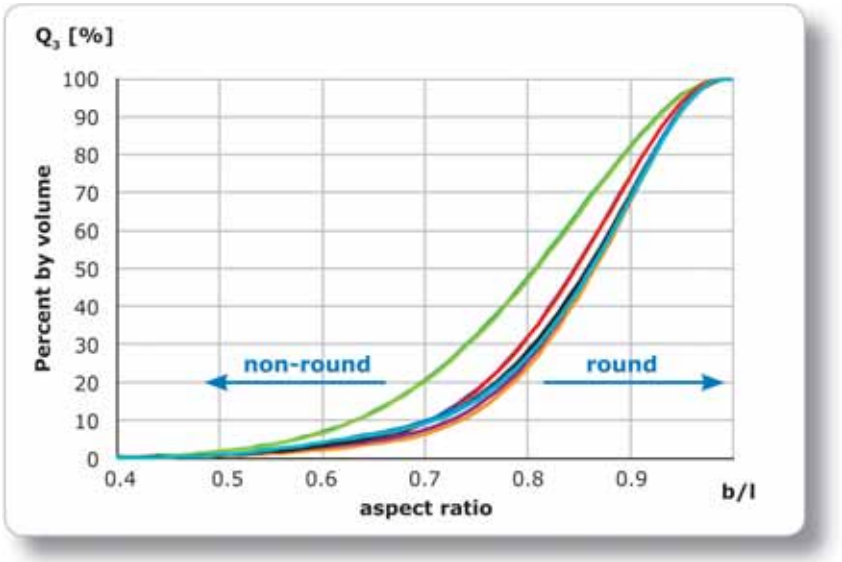

Fig. 6: Aspect ratio of the samples measured in fig. 5. Round particles are plotted towards the right hand side, whereas elongated particles, such as fibers or crystals, are plotted towards the left side of the diagram.

3. CONCLUSION

Seeing is believing: instead of "calculating" particle size distributions from indirect size measurements, the DIA method provides precise, direct information of each particle about its length, width and shape. In addition to the calculated and averaged numbers for the size distribution, the images of the particles are available to get an "impression" of the sample size and shape, like in a microscope, but optimized to measure millions of particles in a short time. Dynamic Image Analysis provides faster and more accurate information than the established methods and is therefore ideally suited for the quality control of pharmaceutical products.

References:

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2. Grant Heinicke, Frank Matthews, Joseph B. Schwartz, „The Effects of Substrate Size, Surface Area, and Density on Coat Thickness of Multi-Particulate Dosage Forms", Pharmaceutical Development and Technology, 1:85-96, 2005

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