HORIBA Scientific

Application Note

CAMSIZER® Pharmaceutical Globules

AN142

Determination of the Roundness of Globules in the Pharmaceutical Industry

The determination of grain size and roundness of globules and other vehicles in the pharmaceutical industry is of special interest. This is because the active substance content of the finished globules and functional drugs correlates with their grain size or layer thickness. In addition, the shape of the globules is one of the deciding factors for further usability, for example in dosing dispensers. For controlling these quality characteristics quick, objective measurement methods are required which guarantee high analytical accuracy as well as a high product throughput.

Introduction

Small round particles (globules) are widely used as a delivery device for medicinally active substances. Saccharose is often used as the base substance. The sugar crystals are formed into globules by means of a complicated building-up process. Alcoholic solutions of the specified active components are then used to introduce the material into the finished globules by absorption.

Globules are manufactured to size specifications according to their uses, covering a certain grain size range. Testing of whether the globules correspond to this grain size range is still usually carried out by means of sieve analyses.

Apart from the grain size, the grain shape is also important for further use of the globules. Convenient dosages for the user, for example from dispensers, require particles which are as round as possible, since globules which deviate considerably from a spherical shape may get stuck or be destroyed by the dosing mechanism.

A fast, objective measurement method for characterizing size and shape to eliminate systematic errors is required to improve throughput and statistical validity.

Measurement principle

The CAMSIZER® analyzer provides rapid, accurate and repeatable size and shape measurements of samples such as these.

Fig. 1: Product photo - CAMSIZER®

The globules are added through a sample funnel and passed to the measuring equipment by means of a vibrating chute. The particles fall individually in front of the light source and (see figure 2) are photographed by two high resolution matrix cameras with different image scales.

Fig. 2: Measurement system

From the shadow projections captured by the cameras, each particle is scanned in 32 directions by the software to provide a high-resolution measurement of the size of the particles, as well as the particle shape. The sample material is collected in a tray and can be retained for further testing or other uses.

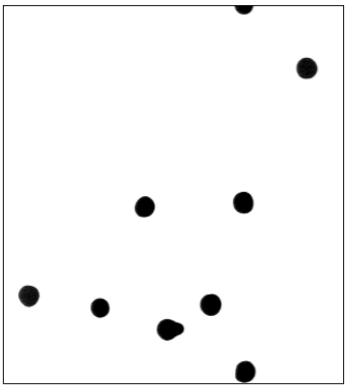

Fig. 3: Instantaneous photographs during measurement

Through the patented two-camera technology, a measuring range of 30 µm to 30 mm is possible without requiring any optical adjustments. Several thousand globules per minute can be measured, so that the CAMSIZER® guarantees very high statistical reliability of the analytical results, together with short measurement times.

CAMSIZER® Sieve Correlation

An essential requirement for new techniques is correlation of the results with those obtained from traditional sieve analysis. This is necessary since a large body of historical data will have been generated and changing specifications based on a new measurement technique can require a significant amount of work.

Correlation between the two different analytical methods is guaranteed by the software of the CAMSIZER®. Thus specifications derived using sieve analysis can be directly adopted. A comparison of the CAMSIZER® results with those from sieve analysis on the basis of a sample measurement is represented in the graph below.

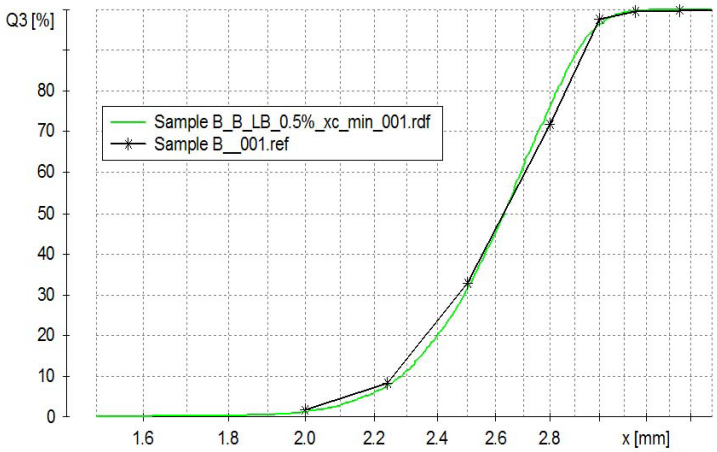

Fig. 4: Comparison of CAMSIZER® result with sieving

The green curve shows results from the CAMSIZER® measurement and the black curve the result of sieving for the same sample.

The grain size spectrum of the globules extends here over a range from 2 mm to 3 mm. Agreement of the results from the two measurement methods is excellent. However, strictly speaking the sieve analysis only gives information on the grain size distribution of the sample at the sieving points. These points are shown by black asterisks on the curve.

CAMSIZER® Resolution

For samples with a narrow grain size distribution, normally only a few analysis sieves are available, so that resolution of the grain size distribution by sieve analysis is only poor. In contrast to this, with the CAMSIZER® the grain size analysis can be carried out in up to 10,000 size classes. After measurement, the results can also be represented in the well known sieve classes, or in up to 50 freely definable size classes. Thus the resolution from a grain size spectrum determined with the CAMSIZER® is very much higher than sieving.

Additional problems arise with the sieving method through sticking of the sample particles in the sieve mesh as near-mesh-size grains (see figure 5), which prevents smaller particles from passing through the wire mesh of the sieve. The result of the analysis is thus displaced into the coarse range, and the measured values are inaccurate.

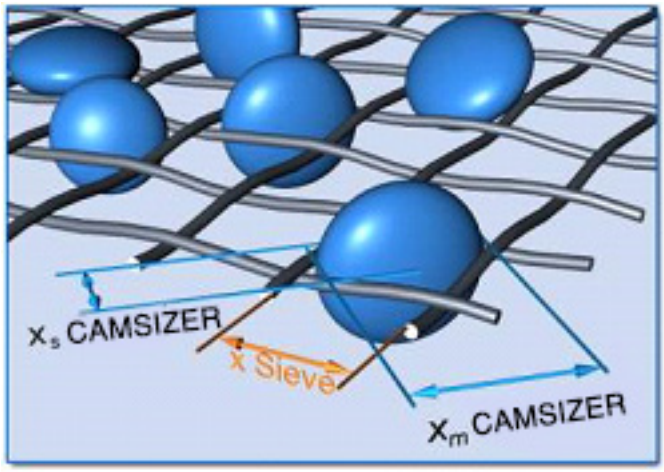

Fig. 5: Danger of false results through clogged sieve wire mesh (blinding)

In such cases the quantity of sieved material must be reduced; however this in turn reduces the meaningfulness of the sieve analysis.

On the other hand, with the CAMSIZER®, any sample quantity can be measured, since the particles do not interfere with each other, providing an accurate and statistically reliable measurement . The measuring time for a typical sample size of 150 mL is approximately two minutes. Compared with the time necessary for a complete sieve analysis, this represents a considerable time saving.

However, the possibilities for grain size analysis with the CAMSIZER® are by no means exhausted here. Thus, further application possibilities exist, for example, in the monitoring of coating processes. In this process the high-resolution grain size determination makes it possible to compare untreated and coated material. In this way the layer thickness can be determined from measurements taken between the production steps, and the process efficiency controlled.

High-Resolution Shape Analysis – without additional time requirements

Grain shape is measured with the CAMSIZER® at the same time as the grain size analysis. In this process the user can not only obtain a result for grain shape in relation to the particle size, but also in relation to the proportions of round and out of round particles. In this way samples can be directly compared with each other with regard to their grain shape properties.

An organoleptic assessment with the human eye is much poorer as an alternative method since the fluctuations in such results can be very high, and furthermore this takes considerable time. Subjective visual assessment of the grain shape with the human eye depends on the size and color of the sample material, on the quality, which has been examined immediately beforehand, and also on the way the working area is illuminated.

With other digital image processing systems that work with a static sample, generally only a few globules are measured in comparable time periods and therefore provide only a poor representative measure of the complete sample. For example, through preferred orientation in static image analysis, broken or flat lenticular particles are not registered at all since the 3rd dimension of the thickness is concealed.

Figure 6 shows a comparison between two samples. In the graph, the roundness (SPHT = spherical geometry) of the particles is plotted as the abscissa. The number of samples having less roundness than a specified value can be read on the ordinate. A perfectly spherical particle is allocated the SPHT value 1. The more the out of roundness of the particle, the lower the roundness value.

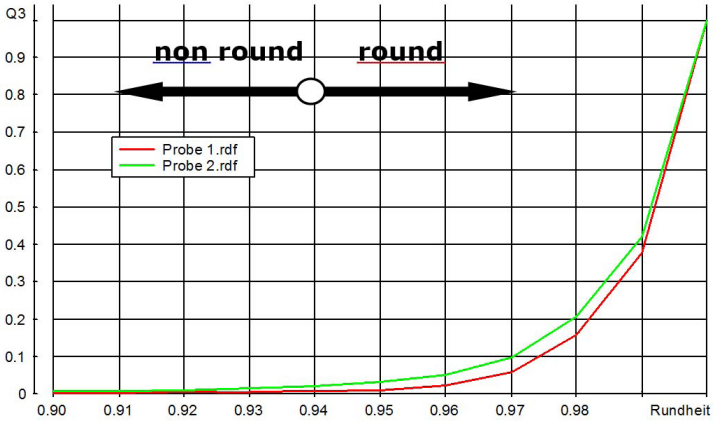

Fig. 6: Comparison of the roundness of two samples

For sample 2, approx. 20% of the sample has a roundness value of less than 0.98. On the other hand for sample 1 this applies to only approx. 17% of the sample. Accordingly, sample 1 (red curve) is more round. This simple criterion can provide a quick and accurate assessment of the samples.

In developing the measurement method, an internal standard is first defined with which all samples tested are then compared. If a sample is situated on the left hand side of the standard in the graph, the sample is less round. A new definition of this standard owing to changed quality requirements is easy and requires no further measurements to be taken. Direct output as a quantile is also possible (Q3 (SPHT=0,98) = 20.0%).

Conclusion and Future Prospects

The CAMSIZER® digital image processing system can be used to replace traditional sieve analysis in measuring free-flowing bulk materials in the pharmaceutical industry without any problems. The short measuring time and high precision measurement of grain size and shape makes it possible to analyze a large number of samples in the shortest possible time, therefore guarantying optimum quality control.

In the monitoring of coating processes, additional application possibilities are possible through high resolution grain size determination together with measurements of the layer thickness between coating steps. Research with the CAMSIZER® is currently being carried out involving the measurement of grain size, grain shape, specific surface and apparent density of functional drugs.