Particle Size Analysis for the Pharmaceutical Industry

Relevant for: pharmaceutical industry, laser diffraction, particle size distribution, lactose

Particle size strongly relates to flowability, content uniformity, bioavailability, dissolution and absorption behavior, which are crucial parameters in the pharmaceutical industry. Hence, product effectiveness as well as production processes are influenced by particle size, making it important to characterize both active components and excipients. Here, we measure the particle size and distribution of three lactose powders destined as an excipient for different pharmaceutical applications.

1 Introduction

Particle size is a crucial parameter in the pharmaceutical industry, because it influences surface area and porosity and, hence, has an impact on bioavailability, effectiveness and shelf life of a drug. Therefore, particle size is not only monitored in quality control, but also in the development of new active pharmaceutical ingredients (APIs). In fact, particle size distribution (PSD) is among the most important parameters to check when evaluating new drugs. E.g. particle size is critical for powder inhalers that are commonly used in the treatment of various lung diseases to deliver the corresponding API as a powder to the lungs. The drug is prepared as a powder and is inhaled without the need of any propellant gas. The API can be applied in pure form or adhered to a carrier material, such as lactose (1).

Particle size also greatly affects tableting and granulation processes. On the one hand, small particles aid dissolution, but are also more sensitive to overcompression, leading to hard tablets which barely disintegrate. Large particles on the other hand, lead to better flowability, compressibility and feeder clearance during the manufacturing process. Moreover, a more homogeneous distribution is achieved, if particles exhibit a narrow particle size distribution (2).

PSD influences not only the production process and the behavior of a drug, but also the administrative efforts. Namely, a narrow PSD facilitates the specification of new drugs in respect to the FDA process validation guidelines and the International Conference on Harmonization (ICH) guideline Q6A (3) (4).

In this application report we measured the PSD of different samples of lactose. Lactose (α - lactose) is a disaccharide consisting of galactose and glucose, showing great flowability and compressibility. It is used as an excipient for tableting, filler for capsules or carrier powder in inhalers in the pharmaceutical industry (5).

Laser diffraction is one of the most common techniques for particle size analysis, based on the observation that the angle of laser light diffracted by a particle corresponds to the size of the particle. This measurement technique is in accordance with the US and European pharmacopeia (USP 429, EP 2.9.31), which gives guidance concerning laser diffraction methods used for particle size measurements in the pharmaceutical industry.

2 Experimental Setup

Three different lactose samples for different pharmaceutical purposes were tested:

- **Sample 1:** lactose powder with very low particle size for powder inhalers.
- **Sample 2:** finely ground lactose powder used as filler material for wet and dry granulation.
- **Sample 3:** more coarsely ground lactose powder used as filler for capsules, mixtures and triturations.

The measurements were carried out by the means of laser diffraction using a PSA 1190 in dry mode equipped with Dry Jet Dispersion (Venturi dispersion). Each sample was measured with three consecutive measurements. The detailed instrument settings can be read from Table 1.

Input Parameters and Method	
Approximation	Fraunhofer
Measurement time [s]	5
Air pressure [mbar]	50
Vibrator frequency [Hz]	57
Vibrator duty cycle [%]	50

Table 1: SizeExpert settings used for dry mode measurements of lactose samples 1 – 3.

3 Results and Discussion

3.1 Sample 1

Figure 1 displays the overlay of the three particle size distributions of the lactose sample used for powder inhalers measured in dry mode. The volume-weighted D values and relative standard deviations (RSD) are shown in Table 2. The measurement returned a very narrow particle size distribution, which is an important parameter for powders used in pharmaceutical industry.

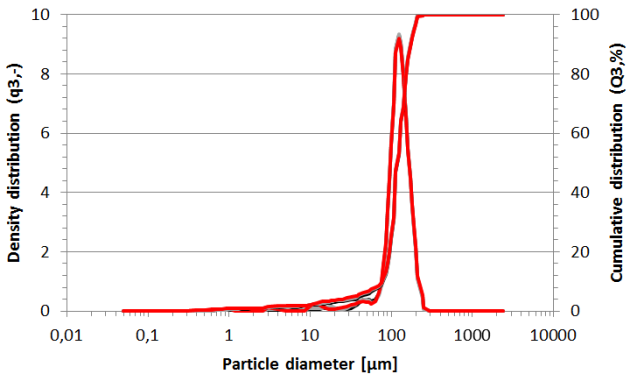

Figure 1: Overlay of the particle size distributions of three consecutive measurements of Sample 1 measured in dry mode

	D10 [µm]	D50 [µm]	D90 [µm]	Span
Min. value	81.28	127.08	180.79	-
Max. value	83.56	127.53	182.71	-
Mean value	82.53	127.27	181.77	0.78
Rel. standard deviation [%]	1.40	0.18	0.53	-

Table 2: Volume-weighted D values and relative standard deviations for Sample 1 in dry mode

3.2 Sample 2

Particle size results returned by dry measurements of Sample 2, a finely ground lactose powder, appeared to be slightly lower than those obtained for Sample 1. This sample also shows the desired, narrow particle size distribution. Figure 2 depicts the overlay of the obtained particle size distributions. The volume-weighted D values and relative standard deviations (RSD) are detailed in Table 3.

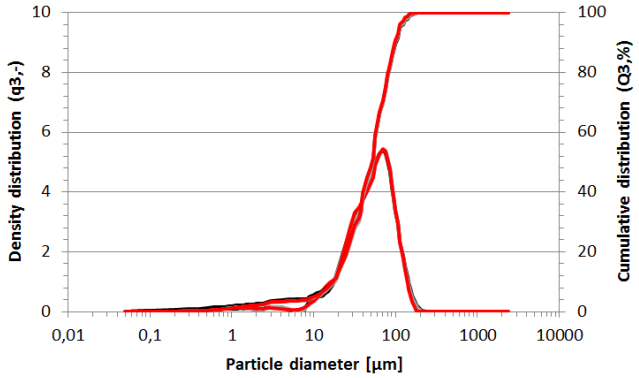

Figure 2: Overlay the particle size distributions of three consecutive measurements of Sample 2 measured in dry mode

	D10 [µm]	D50 [µm]	D90 [µm]	Span
Min. value	18.25	54.65	104.06	-
Max. value	19.11	55.59	106.85	-
Mean value	18.66	55.19	105.60	1.58
Rel. standard deviation [%]	2.31	0.88	1.34	-

Table 3: Volume-weighted D values and relative standard deviations for Sample 2 in dry mode

3.3 Sample 3

Figure 3 displays the measured particle size distributions of Sample 3. As expected, this sample returned the largest particle size, since the lactose is coarsely ground. However, the distribution still stayed narrow. The volume-weighted D values and the respective deviations between the measurement results are shown in Table 4.

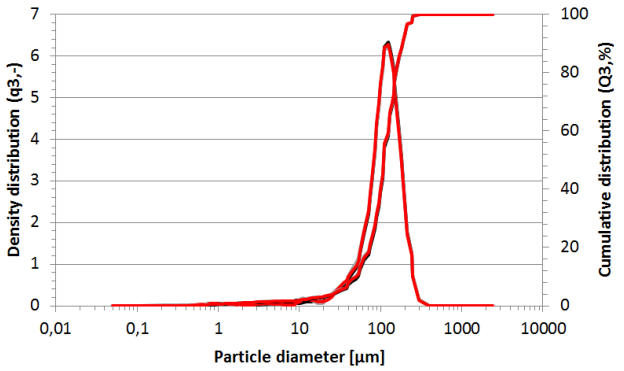

Figure 3: Overlay the particle size distributions of three consecutive measurements of Sample 3 measured in dry mode

	D10 [µm]	D50 [µm]	D90 [µm]	Span
Min. value	52.18	117.94	196.06	-
Max. value	55.37	119.46	197.00	-
Mean value	53.59	118.48	196.25	1.20
Rel. standard deviation [%]	3.04	0.72	0.35	-

Table 4: Volume-weighted D values and relative standard deviations for Sample 3 in dry mode

4 Conclusion

Since particle size greatly influences the properties of APIs and excipients, it is especially important to optimize and monitor the particle size distribution. Here we demonstrate that the PSA instruments are able to deliver highly repeatable measurement results for lactose powders in dry mode. The measurements report clear differences between the lactose powder samples depending on their intended use in pharmaceutical applications. The PSA series proved to be an excellent system for measuring powders using the Dry Jet Dispersion. The PSA instrument and its accompanying 21-CFR-compliant software Kalliope are a reliable partner in particle analysis for the pharmaceutical industry.

5 References

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Measurements: Giorgia De Matteis
Text: Carina Santner

Contact Anton Paar GmbH
Tel: +43 316 257-7129
pc-application@anton-paar.com
www.anton-paar.com