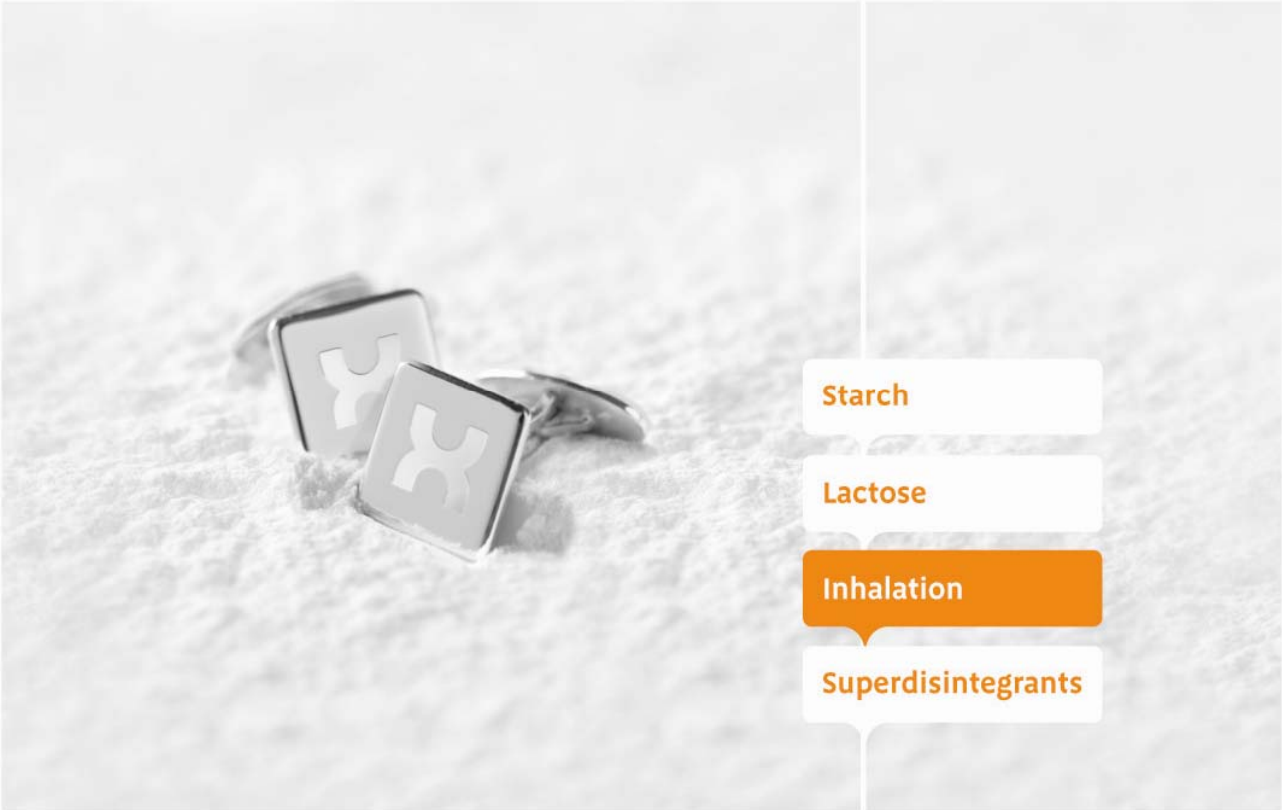
DFE pharma

Particle size measurement of lactose for dry powder inhalers



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1 Introduction

The particle size of lactose has been shown to be important for dry powder inhalers (DPI) [1,2]. Therefore it is important to use robust techniques for the measurement of the particle size of lactose.
In this paper, various aspects for the determination of the particle size of lactose for dry powder inhalers are discussed. For reliable results it is important to take representative samples and to have an exchange of the particle size method between supplier and user.

2 Sampling

Particles in bulk will segregate due to movement of the powder. It is essential that the sample taken is representative for the bulk. In ISO 14488:2007 relevant information for sampling are described. Sample spoons are recommended for taking representative samples [3].
The size of the sample for particle size testing is related to the test method used and the particle size it selves. Sieve analyses require bigger sample size then laser diffraction techniques. Coarser material also need bigger sample size to be representative for the bulk.

3 Testing particle size distribution

Various techniques could be used for measuring the particle size. Sieve analysis and laser diffraction are used for the particle size analysis for inhalation lactose. Laser diffraction is a rapid technique that describes almost the full profile. Sieve analysis generates a limited amount of data. Sieve analysis is often used in combination with laser diffraction to guarantee the absence of coarse particles in the lactose.

3.1 Sieve analysis

Various sieve analysis techniques exists for the particle size measurement of lactose. Sieving could be done by vibration sieves or with air-jet sieving. With one sieve two fractions are obtained, a fine and a coarse fraction. By weighing the weight distribution can be calculated. More sieves can be used in the size range of the product to get a better overview of the full particle size distribution. Sieves can be calibrated with reference materials with a know particle size distribution.
Vibration sieving works well with coarse and granulated lactose. Fine powders will lock the sieve holes. Therefore air-jet sieving works better for finer lactose grades. A disadvantage of the air-jet sieving is that only one sieve screen at a time can be operated.

3.2 Laser diffraction

In the Unites States Pharmacopeia (USP) General Chapter <429>[4] it is stated that laser diffraction involves the measurement of “a representative sample, dispersed at an adequate concentration in a suitable liquid or gas”. For the measurement the powder is passing a laser beam. The light of the laser beam is diffracted in different directions and the scatter pattern is recorded by detectors. The scatter pattern is strongly related to the particle size and the size distribution of the particles. Theories have been developed which quantitatively relate the scattering pattern to the particle size distribution. In ISO13320:2009 the theories are described [5]. The result of laser diffraction techniques is often expressed as a volume distribution. In Figure 1 a particle size graph of Lactohale® 200 is plotted. The full profile is often evaluated and the particle size is often specified as a three point specification containing d10, d50 and d90 value. Also the amount of fines % below 5, 10 or 15 µm could be part of the specification. These parameters are often linked to product performance.

For inhalation lactose the most common laser equipments used are supplied by Sympatec and Malvern. The lactose can be dispersed dry or in a suitable liquid e.g. iso-octane or saturated iso-propanol. The preferred method is the dry-dispersion technique.

The method between supplier and users should be consistent, validated, understood and shared. This is necessary to understand the outcomes of a measurement. It is helpful to investigate the off-set between machines and laboratories by carrying out a round-robin. The results give a better understanding of the outcomes of a measurement.

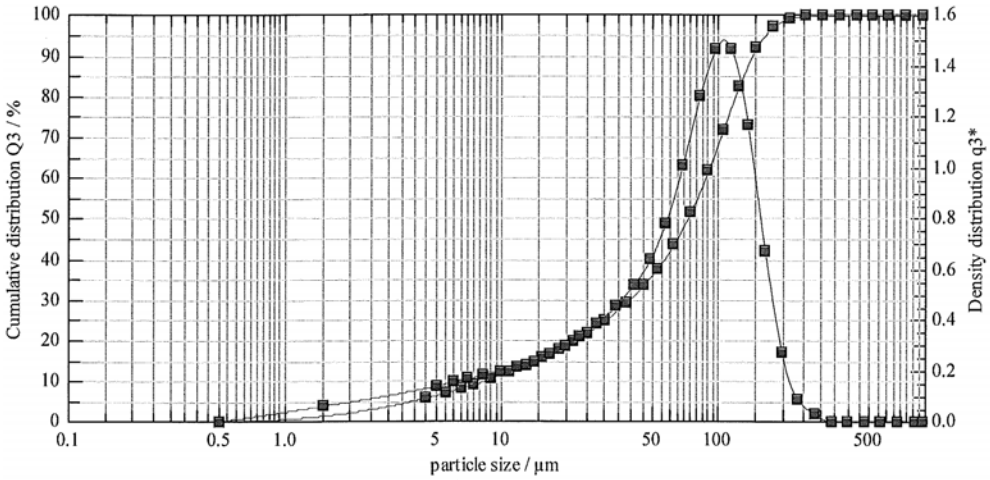
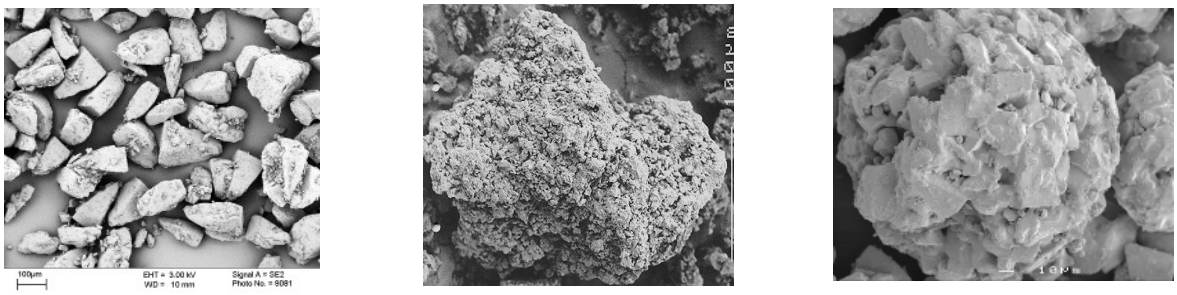


***Figure 1**: Laser diffraction pattern of Lactohale® 200.*

3.3 New techniques for particle size characterization

Recently new equipment has become available that is able to measure the particle size together with the particle shape. In this way the particle size can also be expressed in other distributions like Ferret diameter and elongation ratios. Morphologi-G systems of Malvern and Qicpic of Sympatec are examples of these equipments. These techniques make it possible to obtain a deeper insight in the shape of the particles and the shape distribution of the particles.

Techniques like microscopy and image analyses can be important to be used in combination with laser diffraction techniques. Sieved α-lactose monohydrate crystals typically have a tomahawk shape (Figure 2a). The milled α-lactose monohydrate particles are typically irregular tomahawk shaped with fine particles on the surface. Sieved and milled anhydrous β-lactose is irregular shaped (Figure 2b). Whereas, the particle shape of spray-dried lactose is spherical containing an irregular surface (Figure 2c).



(a) α-lactose monohydrate crystals (b) anhydrous β-lactose (c) spray-dried lactose

***Figure 2:** SEM pictures of different types of lactose.*

4 Conclusion

Different techniques exist to characterize the particle size of lactose. The different equipments in combination with the method used can result in different outcomes on the particle size. Sampling and the method between supplier and users should be consistent, validated, understood and shared.

References

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