Development of a novel laser diffraction method for estimating fine particle fraction of adhesive mixtures

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Summary

A laser diffraction method has been developed for characterizing adhesive mixtures and estimating their fine particle fraction. The method is robust and highly reproducible. A linear correlation was obtained between the cumulative volume of particles < 5 µm and the fine particle fraction of the API AZD8683 formulations measured by the Next Generation Impactor. The method is very fast, in particular when compared to impactor methods, and has the potential to be an important tool for screening of dry powder formulation during development and for in-process control (IPC).

Introduction

Particle size is a key parameter in respiratory drug delivery as only drug particles less than about 5 µm in aerodynamic diameter are able to reach to the peripheral areas of the lungs. Aerodynamic particle size distribution of drug aerosols is routinely measured by sizing techniques based on inertial impaction (e.g. the Multi-stage Liquid Impinger (MSLI), the Andersen Cascade Impactor (ACI), and the Next Generation Impactor (NGI)) and is a well established Pharmacopeia technique. However, impactor analysis is labour-intensive and time-consuming, and is often a bottle-neck in early product development. Particle sizing by laser diffraction (LD) is fast, reproducible and has the potential to be an important tool for rapid characterisation of dry powder aerosol formulations. However, the use of LD to characterise the aerolisation of adhesive mixtures of drug-lactose blends is limited. First, LD is not a chemically differentiating method and can not differentiate between drug and excipients in the produced aerosol. Furthermore, drug and excipient particles differ in shape, refractive index and absorption coefficient which limits the conversion from diffraction pattern into a particle size distribution[1,2]. Nevertheless, using an LD method, one may be able to compare and rank the performance of different formulations which may be useful in formulation screening as well as for IPC purposes.

In this work an LD method was developed and adapted for characterisation of adhesive mixture aerosols using in-house manufactured dispersion tubes. LD results for a series of formulations are presented and compared to the fine particle fractions obtained from impactor analysis (NGI) using a model inhaler.

Experimental methods

A laser diffraction particle sizer (Sympatec HELOS) was adapted using an in-house developed dispersion tube (20 cm long with a diameter of 8.5 mm). Care was taken to minimize recirculation of fine particles and contamination of instrument lenses, e.g. by correct positioning of the dispersion tube and using a high flow vacuum suction[3]. This was found to be crucial at the flow rates used in this study. Prior to an experiment, the air flow rate through the tube was thoroughly adjusted by a regulator and recorded by a digital mass flow-meter (TSI4043). Powder was transferred into the tubes using a spatula and a lid was closed to tighten the tube. Pressurized air thereafter pushed the powder out of the tube, which enabled deaggregation of the formulation. The formed aerosol plume orthogonally intersected the laser beam giving diffraction. The diffracted light was focused onto a 31-array diode detector and the diffraction pattern was converted into a particle size distribution using an algorithm based on Fraunhofer theory. Initial experiments showed that the particle size distribution was independent of the amount of formulation (in the range ~ 5-30 mg).

A series of adhesive mixture formulations were selected, where the fine particle fraction < 5 µm (FPF), as measured by the NGI, was highly dependent on mixing time. The formulation was blended in a high shear mixer and consisted of 5% API (AZD8683), 3% lactose fines, 3% Mg-Stearate (lubricant) and 89% coarse lactose particles as carriers.

Results

In Fig. 1, particle size distributions for ten consecutive measurements from one formulation are shown. Coarse particles appear at diameters of around 60 µm, while fines of lactose and API are seen in the size range ~1-10 µm. As

seen in the figure the measurements are highly reproducible with a relative standard deviation (RSD) in the volume fraction of particles less than 5 µm of only 1.4 %.

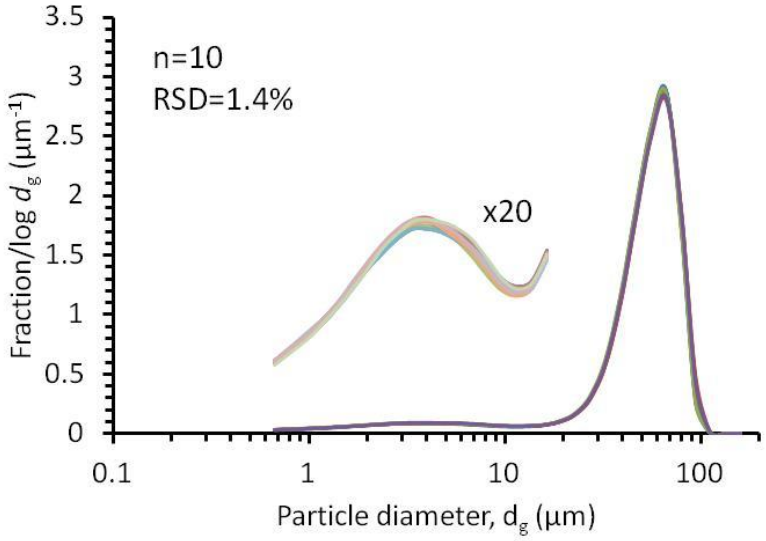

Figure 1 - Particle size distributions for ten consecutive measurements at a flow rate of 60 lmin^{-1}. The formulation was blended 120 min. The size range up to 20 µm is magnified 20 times to better illustrate the reproducibility. The RSD of the volume fraction < 5 µm is indicated in the figure.

The aerosolisation behaviour of the formulations was characterized using flow titration[4] covering the range15 – 100 lmin^{-1}. Measurements were performed by two analysts on two different days to assess the reproducibility and repeatability of the method. In Fig. 2, particle size distributions at three different flow rates are shown. The fraction of fine particles increases with increasing flow rate while the size of the fine aerosol particles decreases with increased flow rate. The volume fraction of particles less than 3, 5 and 9 µm are plotted versus applied flow rate in Fig. 3. The figure shows that the variability is negligible at low flow rates, while results obtained at the highest flow rates (>80 lmin^{-1}) are more variable, potentially due to multi-counting of recirculating particles.

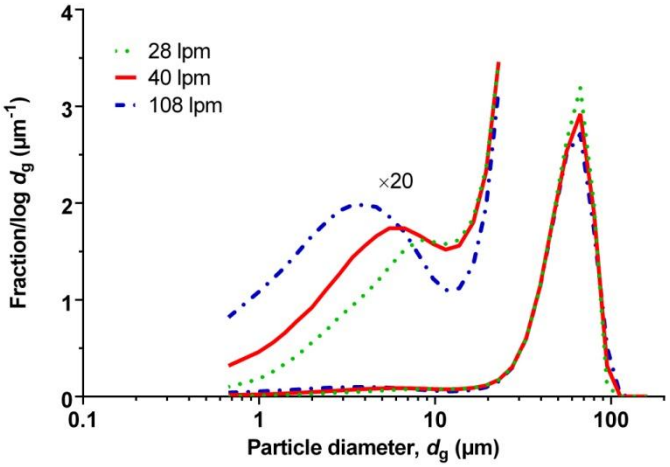

Figure 2 - Particle size distributions obtained at three different flow rates for a formulation blended for 180 min. 100 lmin^{-1} (dash dotted line), 40 lmin^{-1} (solid line) and 20 lmin^{-1} (dotted line).

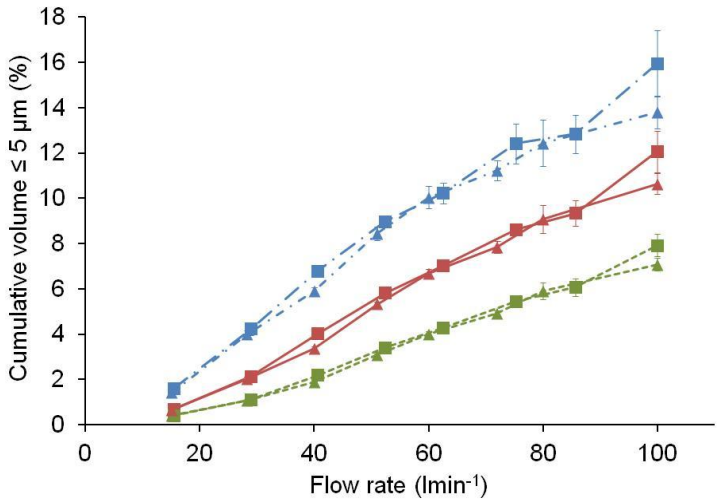

Figure 3 - Fraction of particles less than 9 µm (dash dotted line), 5 µm (solid line) and 3 µm (dotted line), respectively, versus flow rate for an adhesive mixture of AZD8683 blended 180 minutes. ■ Analyst 1 and ▲ Analyst 2. Error bars represent one SD.

The relationship between the volume fraction ≤5 µm determined at 80 lmin^{-1} and fine particle fraction (of delivered dose) from NGI impactor measurements for six formulations differing only in mixing time is shown in Fig. 4. The relation is linear with a slightly better correlation for 72 lmin^{-1} (r^2=0.99) than for 80 lmin^{-1} (r^2=0.98).

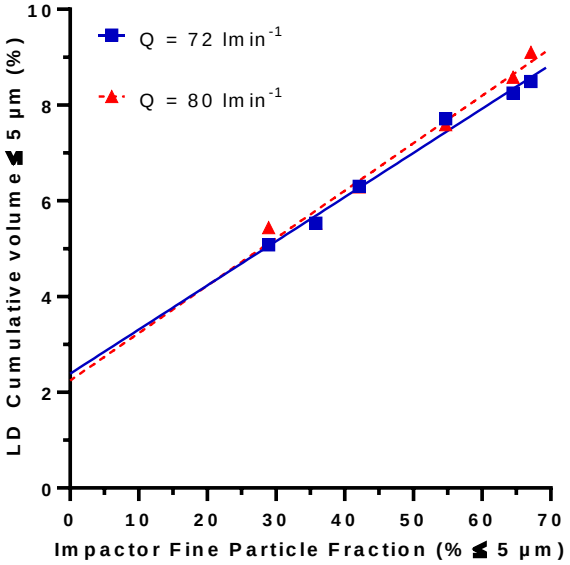

Figure 4 - Volume fraction of fines less than 5 µm obtained by laser diffraction measurements vs fine particle fraction (% < 5 µm) obtained by impactor measurements for six AZD8683 formulations differing only in blending times. Two different flow rates were used in the laser diffraction measurements: 72 lmin^{-1} (■) and 80 lmin^{-1} (▲).

Discussion and conclusion

The developed method is highly reproducible, in particular at low flow rate (<~90 lmin^{-1}) and since no weighing of the powder is needed the method is very fast.

A linear correlation was found between the cumulative volume of all particles < 5 µm determined by laser diffraction dispersed at 72 or at 80 lmin^{-1} and the fine particle fraction for a series of adhesive mixture formulations as measured by the NGI impactor.

We note that the extrapolated regression lines in Fig. 4 give a non-negligible fraction at zero flow rate. The reason for this offset is unknown but we may speculate that this could indicate that the fine particle fraction of lactose fines are less dependent on formulation mixing time than AZD8683 for these formulations. Further studies are currently under way to better understand the deaggregation of lactose fines.

We can conclude that the method clearly has the potential to become a valuable tool for screening of fine particle fraction for adhesive mixtures in development phase as well as for use for in-process control.

Acknowledgements

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References

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