USING LASER DIFFRACTION AS A SCREENING TOOL FOR DRY POWDER INHALER FORMULATIONS

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ABSTRACT

Reproducible drug delivery from dry powder inhaler systems requires control of the delivered drug particle size. Particle morphology is also important as the surface properties of the drug and excipient particles can have a significant effect on the process of deagglomeration that occur within the powder spray plume during inhalation. This, in turn, can define the deposition characteristics of the drug within the respiratory tract.

Traditionally, particle size analysis of dry powder inhaler formulations has been carried out using cascade impaction (CI). However, CI measurements are time consuming, of low resolution and only provide a time-averaged result. In this work a method is presented for measuring the particle size produced by different dry powder formations using the technique of laser diffraction. Rapid data acquisition speeds of up to are possible using laser diffraction, allowing the dynamics of power release to be assessed along with the average particle size. This can aid in understanding the delivery dynamics and can allow different formulations to be rapidly screened for the correct dispersion properties.

INTRODUCTION

Optimisation of the particle size distribution delivered by dry powder inhaler (DPI) devices is an acknowledged and well-recognised aspect of respiratory drug delivery. Less well investigated but still important is the effect of particle morphology. Changes in the surface properties of the drug and excipient particles can have a significant effect on the processes of agglomeration and deagglomeration that occur during inhalation. This, in turn, can define the deposition characteristics of the drug within the respiratory tract.

Traditionally, the fine particle fraction, as measured using a cascade impactor (CI), has been used to assess the performance of different DPI formulations [1]. A CI measures aerodynamic diameters based on inertial impaction and allows the sampled mass to be weighed directly without artificial processing and without dependence upon statistically manipulated data. A downside to the use of CIs is the need to operate the device being tested many times to minimise experimental error. Measurements also tend to be time consuming, of low resolution and only provide time-averaged size distributions at a fixed flow rate.

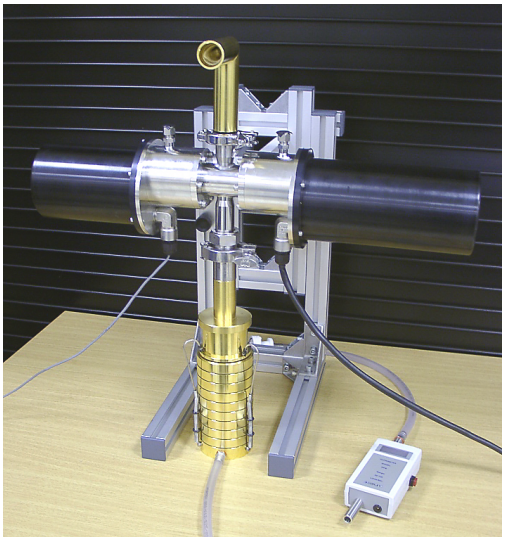

Figure 1. Spraytec Inhalation cell placed in-line with a Andersen-type cascade impactor.

Laser diffraction particle sizing offers an alternative technique for the rapidly screening of different DPI formulations. Data acquisition speeds of up to 2500Hz (one measurement every 0.4ms) are possible using laser diffraction. The dynamics of powder release from the DPI can therefore be assessed, allowing the discrimination of the diffraction patterns produced by different parts of aerosol cloud such as primary drug particles and aggregates, carrier particles and drug particles delayed by adhesion to the inhaler walls. These results can then be compared with the time-averaged aerodynamic size results obtained using the CI. In this case the technique has been applied to understanding the changes in drug dispersion observed due to changes in the drug-particle morphology.

CHARACTERISATION OF DRY POWDER INHALERS USING LASER DIFFRACTION

A laser diffraction measurement device has been developed by Malvern Instruments Ltd., which is compatible with standard respirable drug testing equipment [2]. Measurements are made in an enclosed cell, allowing the flow rate within the measurement zone to be carefully controlled (Figure 1). This cell can be mounted either before or after a standard USP throat. Measurements can be made in parallel with a CI, allowing comparisons to be made between the MMAD and the MMD reported by laser diffraction.

Experimental

The Malvern Spraytec inhalation cell was installed in-line with an Andersen-type cascade impactor (Copley Scientific). The 100mm Fourier lens is most typically used for inhaler measurements, allowing measurements to be made over a 0.5 to 250 micron range. Measurements were carried out using a data acquisition rate of 2500Hz, with a measurement duration of 2 seconds. The measurements were triggered by monitoring the signal received across the detector elements within the instrument, allowing the measurement to be synchronised with the appearance of the powder plume within the laser diffraction measurement zone. An external vacuum system (Copley Scientific) was used to control the airflow through the system, thus releasing the powder from the DPIs under test.

The DPI formulations tested in this study consisted of powders of salmeterol xinafoate produced by micronisation and by a supercritical fluid precipitation technique (SEDS^{TM} (Nektar, Bradford, UK)). The formulations were prepared with DMV Pharmatose® 325M inhalation grade α-lactose monohydrate excipient and tested in the 13 mm^3 Clickhaler® inhalation device (Innovata Biomed, St. Albans, UK). All aerosols were measured in the throat area immediately before the pre-separator.

RESULTS

Figure 2 shows the time-dependence of the particle size measured for the actuation of an inhaler containing the micronised salmeterol xinafoate formulation.

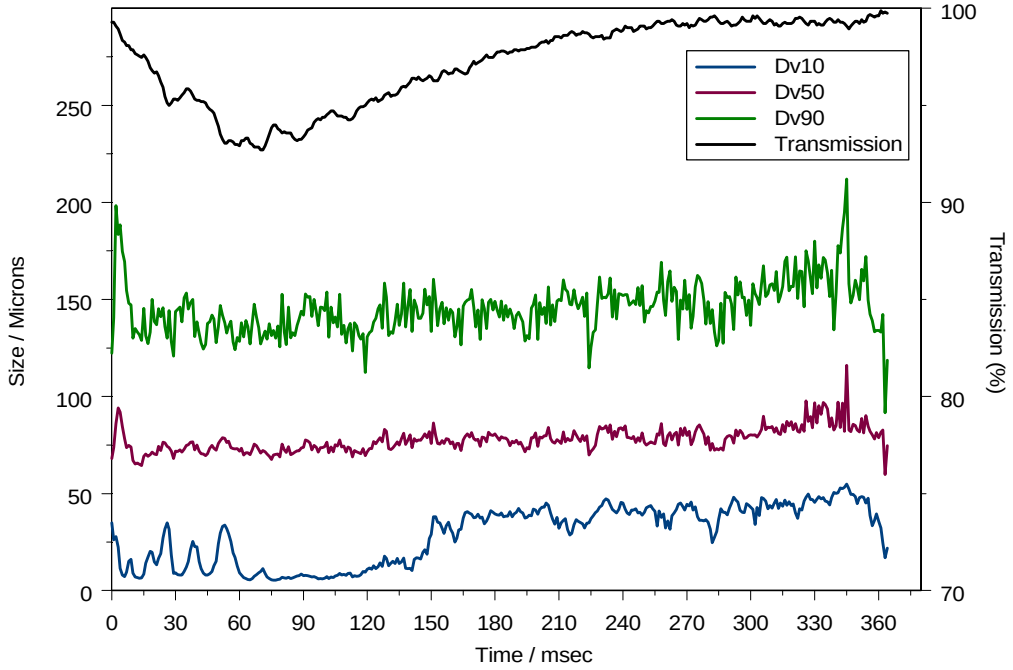

Figure 2: Time-history showing the particle size measured during the actuation of the inhaler containing the micronised salmeterol xinafoate formulation.

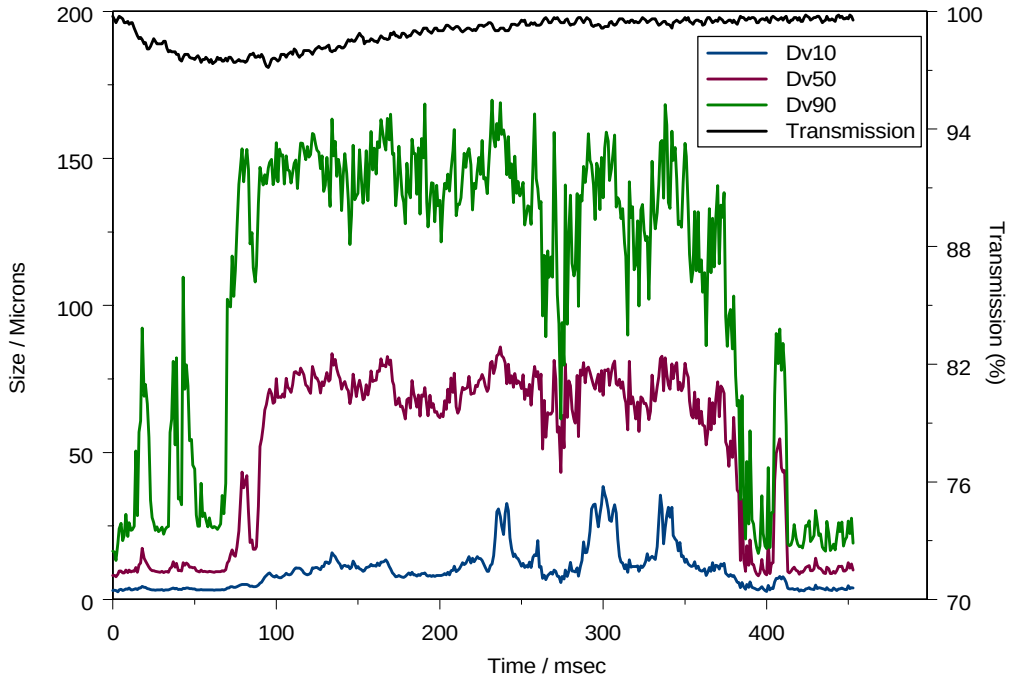

Figure 3: Time-history showing the particle size measured during the actuation of the inhaler containing the SEDS™ salmeterol xinafoate formulation.

In this case the powder was released from the device over a period of 400ms. The results show that the delivered particle size remained relatively constant during the release of the powder, with a mixture of excipient and drug being observed at all times.

Figure 3 shows the results obtained under the same measurement conditions for the inhaler containing drug particles produced using the SEDS™ technique. Separation of the fine drug particles and the lactose carrier was observed in this case, suggesting increased de-agglomeration of the fine drug particles. Dispersed, fine drug particles initially appeared in the measurement zone (0.0sec - 0.07 sec). This is as expected, as these particles will be rapidly entrained in the airflow. During the mid-point of the spray plume (0.07sec – 0.4 sec) a mixture of lactose carrier and fine drug particles was observed. Finally, the tail of the spray plume (0.4sec - 0.45 seconds) contained mainly fine drug particles. It is believed that these particles were delayed by adhesion to the inside of the inhaler.

The increased dispersion observed in the case of the SEDS™ formulation is believed to be related to the particle morphology. The drug particles produced by the SEDS™ manufacturing technique are individual crystallites that are smooth-surfaced, thus aiding dispersion. In contrast, micronised drugs are generally rough-surfaced. This causes the lactose and drug particles to bind more strongly during storage, thus affecting the particle size of the powder plume emitted by the inhaler.

Particle Size Distribution Comparisons

The average particle size distribution delivered for each formulation was calculated by averaging the time-resolved data obtained during the actuation of the inhaler. The distributions recorded for the formulations containing the micronised and SEDS™ drug particles are shown in figure 4, along with the result obtained for a lactose-only formulation. Both the lactose excipient (80-micron mode) and the fine drug particles were detected in each case. Enhanced de-agglomeration of the SEDS™ drug particles was clearly observed, with a higher percentage of material being observed below 40 microns compared to the micronised drug formulation. These observations were supported by in-line measurements carried out using the CI which show that the respirable fraction measured for the SEDS™ formulation was significantly higher than for the micronised product (57.8% compared to 25.5%).

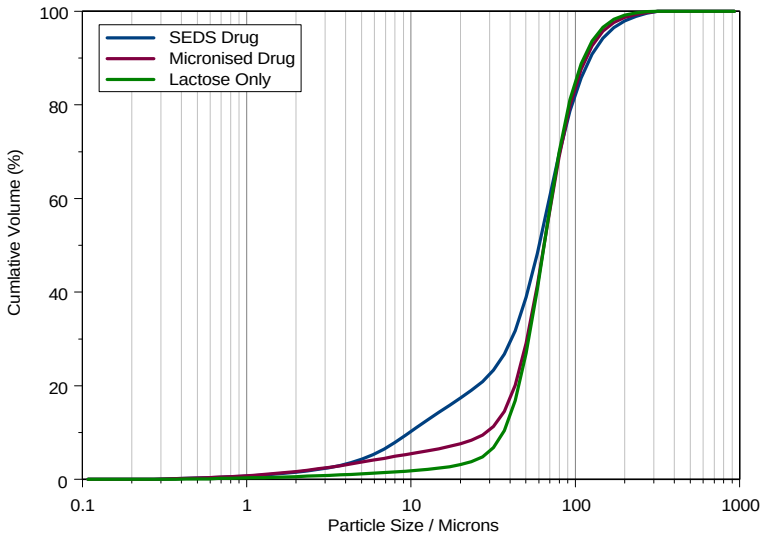

Figure 4: Average particle size distributions calculated for the micronised, SEDS™ and lactose-only formulations.

Pure Drug Formulations

Confirmation of the improved dispersion of the drug particles in the case of the SEDS™ formulation can be obtained by measuring the output of DPIs where no lactose excipient is present. The particle size distributions measured for both the micronised and SEDS™ salmeterol powders are shown in figure 5. As can be seen, the particle size recorded for the SEDS™ drug formulation is much finer than for the equivalent micronised drug, again suggesting that de-agglomeration of the SEDS™ powder is more easily achieved. A good correlation is also observed between the particle size measured for the drug-only formulation and the particle size of the drug particles within the excipient-containing formulations.

CONCLUSIONS

The particle size produced by different DPI formulations was measured using the technique of laser diffraction. The rapid data acquisition speeds possible using this technique allows the dynamics of powder dispersion to be easily assessed. In this case, differences in dispersion were detected for DPI formulations containing micronised and crystalline salmeterol xinafoate drug particles. These differences are believed to relate to the drug particle morphology. Laser diffraction has therefore been shown to provide a means of rapidly screening different formulations during formulation development.

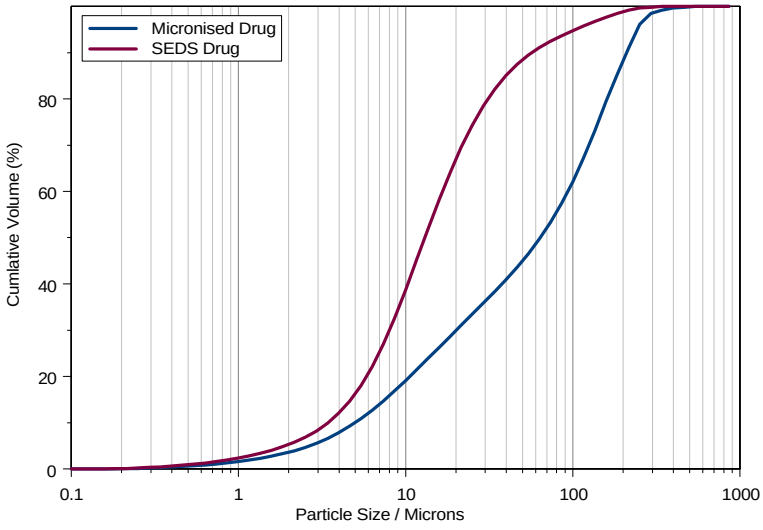

Figure 5: Average particle size distributions measured for the drug-only formulations.

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2. C.E. Homes, P.G. Kippax, H.E. Newell, J.P. Southall and D.J. Ward, Simultaneous Analysis of Respirable Aerosols via Laser Diffraction and Cascade Impaction, *Proc. Drug Delivery to the Lungs X11*, pp. 58-61, 2001.