

# THE MEASUREMENT OF DRY POWDER INHALERS USING THE MALVERN SPRAYTEC

## INTRODUCTION

The delivery of therapeutic agents to the respiratory system via aerosols is a well-proven route for the treatment of asthma and other pulmonary diseases. This has led to the development of a wide range of drug delivery devices, such as nebulisers, MDIs and DPIs. Delivery of drug substances via the lungs has several advantages as it circumvents first-pass metabolism and can yield a rapid pharmacological response which, in some cases, is equivalent to that seen for subcutaneous injection. For this reason the inhalation route is now being considered not only for the treatment of respiratory conditions but also as an important route for the systemic delivery of “fragile” active substances such as proteins and other macromolecules.

A key parameter in defining the efficiency of inhaled drug treatments is the particle size of the aerosol, as this defines the disposition site for the drug within the respiratory tract. The smaller the particle size of the aerosol is, the more likely it is that the droplets will be deposited in the lungs rather than in the mouth or throat. Particles less than 5 microns are known to show significant pulmonary deposition [1]. However, care must be taken to avoid the production of extremely fine particles (size < 0.5 microns) as these may be exhaled. Most aerosol delivery devices therefore target the 1-3 microns size range order to achieve a high delivered dose and therefore the desired therapeutic effect.

## DRY POWDER INHALER DEVELOPMENT

Inhalers based on dry powder formulations have been the focus of much interest over the past decade. Dry powder inhalers (DPIs) have many advantages over

alternative technologies, including:

- Automatic co-ordination of drug release and inhalation (as powder release is initiated by the patients breathing).
- No propellants are required.
- Easier formulation for “fragile” macromolecules.

The most critical attributes of DPI design are the reproducibility of the dose and the delivered particle size distribution. Powders with particle sizes less than 5 microns tend to agglomerate. The use of excipients such as lactose can help to prevent drug agglomeration during storage. However, successful re-dispersion of the drug and excipient is vital during inhalation if targeted drug delivery is to be achieved. The energy for dispersion is generally obtained from the patient's inspiration. It is therefore important that formulators account for the vast differences,

which exist in patient inspiratory flow rate and produce devices which can deliver a high respirable drug fraction across a wide range of flow rates.

## CHARACTERISATION OF DRY POWDER INHALERS

Malvern Instruments has developed an inhalation measurement cell for use with the Spraytec, which allows the rapid characterization of DPIs, MDIs and nebulizers. This cell is compatible with standard respirable drug testing equipment (Figure 1) allowing the device to be mounted either before or after a standard USP throat. Measurements can be made in parallel with a Cascade Impactor, allowing comparisons to be made between the Mass Median Aerodynamic Diameter and the Mass Mean Diameter reported by laser diffraction in relation to the emitted dose and fine particle fraction.

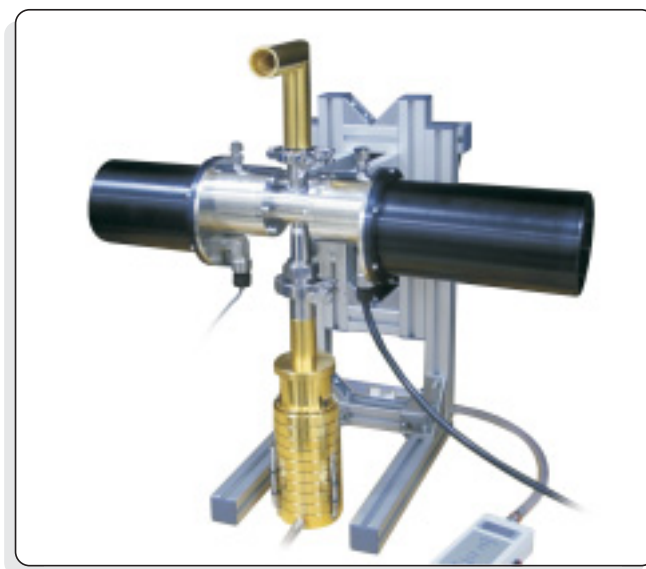


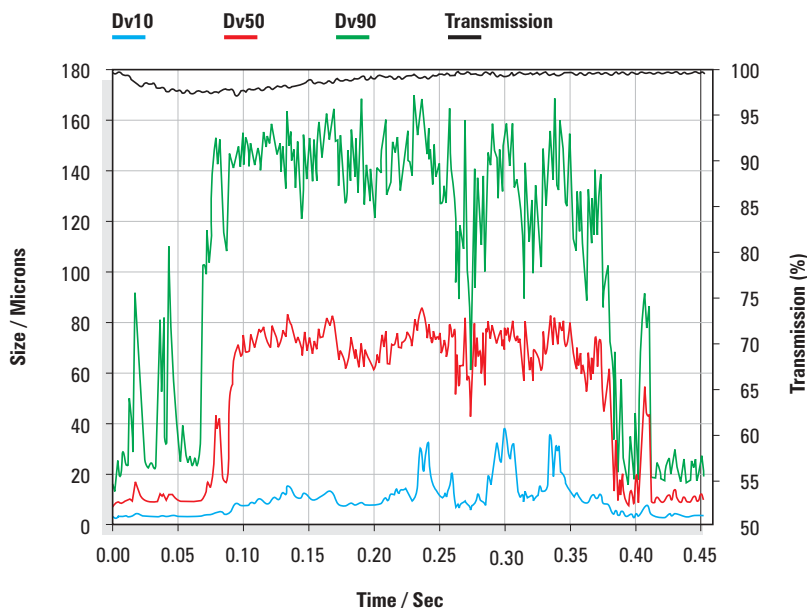
Figure 1: Spraytec with inhalation measurement cell.

## DRY POWDER INHALERS DRUG DELIVERY DYNAMICS

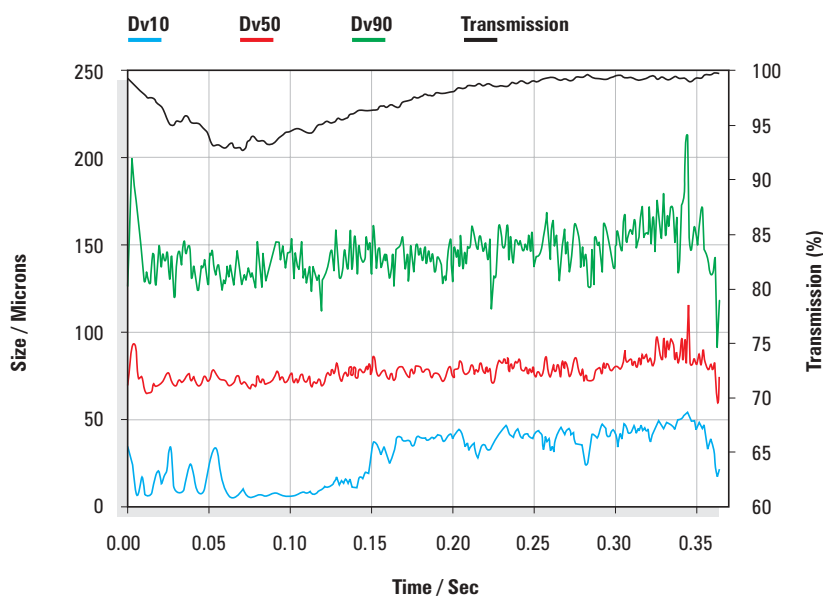
The output of DPIs containing different powder formulations has been measured using the Spraytec inhalation cell. Rapid measurements at 2500Hz can be used to monitor the dynamics of powder release from a DPI, allowing the discrimination of the different parts of the aerosol, such as primary drug particles, aggregates and excipient particles. This can aid in the understanding of the interactions that occur between the drug and excipient particles, along with particle adhesion to the inhaler surfaces. The effect of varying inhalation flow rates on the state of dispersion can also be rapidly assessed.

Figure 2 shows an example of the data obtained for powder release from a standard DPI (formulation A). Measurements were made at a flow rate of 50 LPM, with the aerosol passing through the measurement zone of the instrument in less than 500 milliseconds. The measurement was triggered by monitoring amount of laser light scattering observed on the instrument detectors.

Separation of the fine drug particles and the lactose carrier was observed in this case, with the fine particles appearing in the measurement zone first (0.0sec - 0.07 sec). During the mid-point of the evolution of the aerosol (0.07sec - 0.4 sec) a mixture of lactose excipient and fine drug particles was observed. The end of the aerosol (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. These results are in contrast with those shown in figure 3 for a different formulation (formulation B). Here no separation of the drug and of lactose is observed, suggesting that agglomerate break-up is not so easily attained.



**Figure 2:** Chart showing the variation in the Dv10 (blue), Dv50 (red) and Dv90 (green) measured during the actuation of a DPI (Formulation A). The transmission (black) relates to the concentration of particles in the measurement zone.



**Figure 3:** Chart showing the variation in the Dv10 (blue), Dv50 (red), Dv90 (green) and transmission (black) measured during the actuation of a DPI (Formulation B).

## PARTICLE SIZE DISTRIBUTION COMPARISONS

The average particle size distribution delivered for each formulation can be calculated by averaging the time-resolved data. The distributions recorded for each formulation are shown in figure 4, along with the result obtained for a lactose-only formulation.

In figure 4 both the lactose excipient (80-micron mode) and the fine drug particles are observed. Enhanced de-agglomeration of the fine drug particles is seen in the case of formulation A compared to formulation B.

The reproducibility of the delivered aerosol can also be assessed using the Spraytec system. Figure 5 shows the results taken from two separate actuations of the DPI containing formulation A. As can be seen, the size distributions over-plot showing the reproducibility to be excellent (0.8% RSD based on the reported  $Dv_{50}$ ). Monitoring this over the lifetime of the product will allow the effects of agglomeration and de-mixing within the powder-holding chamber to be assessed.

## CONCLUSIONS

A new device for carrying out laser diffraction particle size measurements has been developed which specifically addresses the testing requirements for respirable aerosols. This system allows for the accurate determination of the respirable fraction produced by a range of different devices including DPIs. In addition, the dynamics of aerosol production during simulated breathing can be determined. The system is therefore a valuable tool is helping in the development of new aerosol-based drug delivery systems.

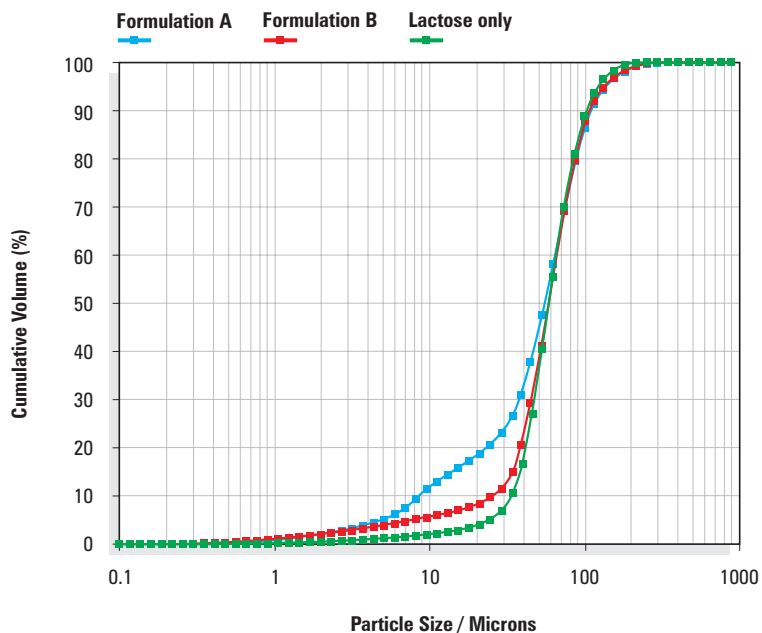
## REFERENCES

1. ISO 13320-1: 1999(E). Particle Size Analysis- Laser diffraction methods. Part 1. General principals.

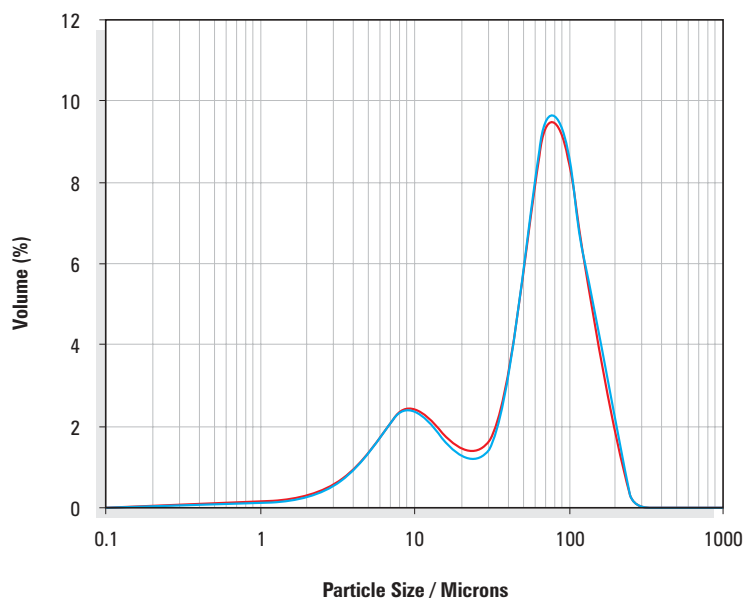
### FURTHER READING:

Spraytec Brochure MRK349

Particle Sizing of Nebulisers using the Malvern Spraytec MRK407-01



**Figure 4:** Chart showing average particle size distribution delivered for formulations A and B. The results for a lactose only formulation are shown for comparison purposes.



**Figure 5:** Particle size distributions calculated for the entire DPI aerosol for formulation A. The size distributions for two separate measurements are shown, illustrating the reproducibility of the sample delivered by the device.

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