Cambustion Application Note DMS04

DMS500 Measurement of Drug Delivery Inhalers

This application note describes the use of the Cambustion DMS500 Fast Particulate Spectrometer to perform real-time studies on the size distribution of fine particles produced by pressurised Metered Dose Inhalers (pMDIs). Example data is given from a Qvar inhaler, a subset of that presented in [1]

Recent studies into adverse effects of exposure to airborne particles have shown that inhaled materials in the ultrafine aerosol form (<100 nm aerodynamic diameter) can exhibit increased toxicity relative to the same material in a coarser aerosol form. For example, Ferin *et al.*[2] conducted a key study in which two groups of rats where exposed to titanium dioxide (TiO_2). A marked inflammatory response was seen in response to the ultrafine TiO_2 but little effect in response to the fine particles. A number of studies have suggested increased efficacy of HFA propelled pMDIs (pressurised metered dose inhalers) over CFC propelled formulations of the same drug[3]. These observations have led some to hypothesise that the physiological impact of ultrafine drug aerosol particles may be greater than the same mass or volume of active agent delivered in a lower number of coarser particles.

The DMS500 has a maximum sampling rate of 10 Hz, and a T_{90-10} time response of 200 ms, so is ideal for temporally resolving the drug release event of a pMDI. It is capable of sizing aerosols in the range 5 nm – 2.5 µm, yielding 16 channels per decade.

A Scanning Mobility Particle Sizer (SMPS) has been used[4] to collect data on the size distribution of fine particles from various pMDIs; however its use is very time consuming as it is impossible to scan the size distribution automatically due to the transient nature of the drug release events compared to the ~ 1 min scan time of the instrument. The instrument has to be manually set to each size class, and the number count from several inhaler bursts is averaged. The DMS500 allows measurement of the size distribution from a pMDI in just a few seconds.

Experimental Method

The setup shown in Figure 1 was used:

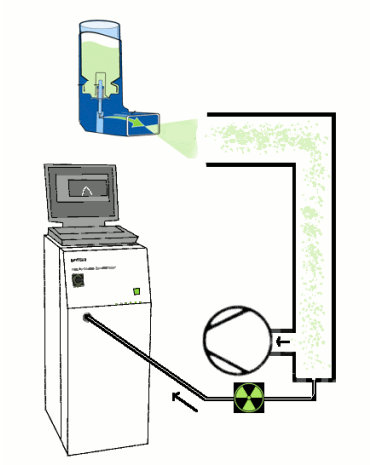

Figure 1: Experimental setup

A USP artificial throat was used to draw in the inhaler spray, in order to simulate impaction at the rear of the throat. The DMS500 draws aerosol at a rate of 8 l/min, and a pump was used to bring the total aerosol flow in the throat to a realistic 28 l/min. A neutraliser (in this case a radioactive source) is essential to remove any pre-existing electric charge on the aerosol particles, as the DMS500 sizes by electrical mobility using its own internal charger. The DMS500 was set to continuously log data at 10 Hz, and the inhalers were sprayed into the throat, leaving approximately 30 seconds between events.

Results

The DMS500 is supplied with a Microsoft Excel add-in which can produce real-time animations from DMS data files, as well as summary data. Data can be weighted by number, area, volume or mass. Real-time lognormal fitting software to summarise data is also supplied (see app. note DMS06).

As an example, Figure 2 shows a contour plot of inhaler bursts from a Qvar inhaler.

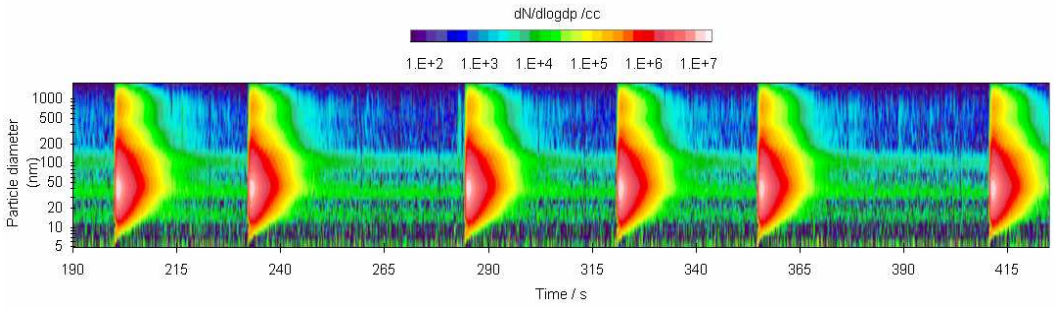

Figure 2: Contour plot of Qvar number weighted size distribution.

Figure 3 shows a single snap-shot of the real-time animation of data from a Qvar inhaler, taken at around 200 s in Figure 2. It shows that within this size range, the number weighted spectrum has essentially one mode, at 45 nm, which does not change in size over the duration of the event. A small side lobe is seen at the beginning.

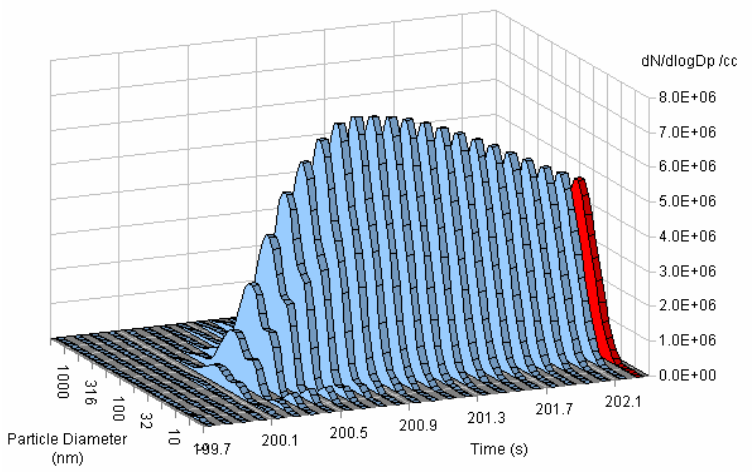

Figure 3: Qvar inhaler, number weighted.

Summary

The DMS500 is a fast, convenient instrument for studies of fine particle production by pMDIs. It offers the fastest time response of any particulate spectrometer on the market today, enabling inhaler events to be clearly temporally resolved.

We would like to thank Mark Crampton of the Division of Environmental Health and Risk Management, University of Birmingham, U.K.

---

[1] *Real-time sub-micron particle size distributions produced by metered dose inhalers*. J. Symonds, M. Crampton, *Lung Modelling: Numerical and Experimental*, University of Sheffield **2004**

[2] *Pulmonary retention of ultrafine and fine particles in rats*. J. Ferin, G. Oberdorster, D.P. Penney, *Am. J. Respir. Cell Mol. Biol*. **6**(5) 535–542 **1992**

[3] *Improvements in delivery with an extra fine beclomethasone aerosol.* R. Davies, *International Journal of Clinical Practice* 28–32 **1998**

[4] *Sub-Micrometer Particle Production by Pressurized Metered Dose Inhalers*. M. Crampton, R. Kinnersley; J. Ayres. *Journal of Aerosol Medicine* **17**(1), 33–42 **2004**