MODEL 3321 AERODYNAMIC PARTICLE SIZER® SPECTROMETER RAPID TOOL FOR ACCELERATED INHALER DEVELOPMENT

APPLICATION NOTE APS-004

Looking for Faster Product Development?

The aerodynamic diameter of a pharmaceutical aerosol determines where and how efficiently the drug will deposit in a patient's lung, and is thus an important parameter affecting performance of inhalation devices. Aerodynamic size distribution tests are widely used during the development of these devices and are a mandatory test prescribed by the regulatory agencies. Inertial size-separation by cascade impactors has been used as the 'gold standard' to aerodynamically size-analyze inhaler-derived aerosols for many years. This method involves collection of aerosol sample on substrates with subsequent chemical analysis of the collected material. Unfortunately, the cascade impactor tests are extremely time consuming (approximately 2 to 4 hours for the preparation and analysis of a test). Furthermore, due to the nature of chemical analysis, the results are usually not available until at least a day after the test is conducted, and the entire process is labor intensive. During the development of inhalation devices, typically hundreds of formulations are screened before the final product is developed. Alternative fast and more convenient tools are desired to speed up the product development process.

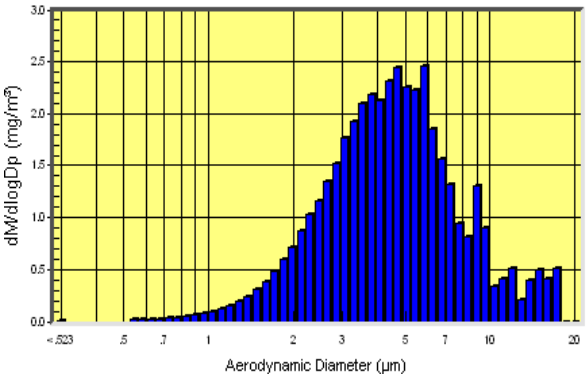

Figure 1. MDI output measured by the APS.

The APS Spectrometer is the Solution

The Model 3321 Aerodynamic Particle Sizer® (APS™) spectrometer is an attractive alternative to cascade impactors or impingers for rapid screening of particle size distributions of inhaler-generated aerosols. The APS operates effectively in the range of greatest interest for inhaler testing (0.5 to 20 µm aerodynamic diameter) and requires just a few seconds for a complete on-line measurement. Using patented time-of-flight technology*, the APS provides significantly higher size resolution (32 size channels per decade) to the cascade impactors (typically 6 size channels per decade), and is highly sensitive in detecting small changes in particle size distributions. This is particularly important when studying the effect of subtle changes in formulations on the inhaler output.

The APS measures number-weighted size distributions which are converted to mass- weighted size distributions (Figure 1) by the data management software supplied with the instrument (this conversion is based on user input particle density). The software generates a statistical report automatically for each measurement with parameters like mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). The instrument is compatible with TSI's Model 390069 data merge software with advanced curve fitting options. When desired the Model 3306 Impactor Inlet with a USP throat can be used in conjunction with the APS (Figure 2) to collect respirable or fine particle fraction (FPF) of the drug on a filter for subsequent chemical analysis.

Figure 2. Model 3321 APS spectrometer shown with Model 3306 Impactor Inlet.

* United States Patent Number 5,561,515

Comparison Results with Cascade Impactors

During the last decade or so, a number of inhaler product development efforts have utilized the APS spectrometer. Many of these studies have reported excellent correlations with traditional cascade impactor results. Inertial impactors are the 'only' method currently written into the US and European pharmacopeias. Consequently, size analysis reports for the final product submitted to the regulatory agencies must be based on impactor tests. It is therefore important for any alternative method used for convenience and speed during the drug development process to correlate well with the cumbersome cascade impactors. Following section provides a brief review of selected studies conducted by independent researchers utilizing the APS spectrometer for metered dose inhaler (MDI) and dry powder inhaler (DPI) characterization.

Metered Dose Inhalers (Solution Formulations)

Stein et al. (2003) investigated factors influencing the size distribution from solution MDIs using the APS. Steven Stein reports ***"the MMAD from size distribution measurements of the APS 3321 closely followed the expected theoretical response to the concentration of the model drug. This experiment would have been excessively large for a cascade impactor testing protocol, however, the APS spectrometer allowed for testing of a large number of configurations with a number of replicates".*** Recently the same group utilized the APS to investigate the influence of atomization and evaporation on MDI drug delivery efficiency (Stein and Myrdal, 2006), the group continues further investigations with the fast and handy APS.

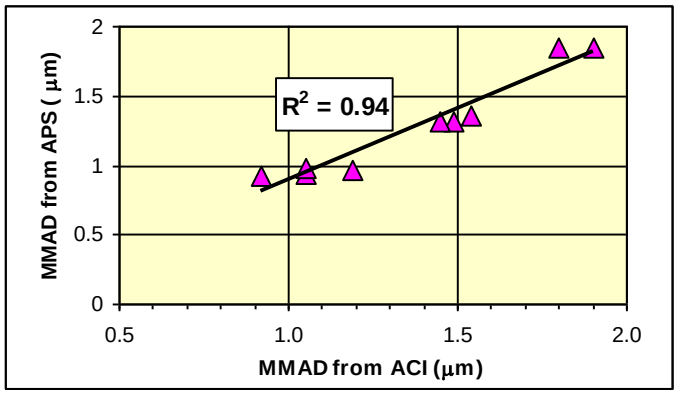

Figure 2. Data shown for MDIs containing HFA-134a beclomethasone dipropionate solution formulations. ACI stands for Anderen Cascade Impactor (Figure adapted from Stein et al., 2003)

Metered Dose Inhalers (Suspension Formulations)

Another group of researchers at 3M drug delivery systems led by Ma Jingwen evaluated the performance of APS for rapid screening of MDI suspension formulations containing non-volatile excipients (Jingwen et al., 2006). The researchers successfully used curve fitting to segregate modes from drug and excipient particles for formulations with low and moderate excipient concentrations. The authors note that under most circumstances when an excipient is used as suspension aid, APS can be used as a rapid screening tool in an accelerated stability study. The study concluded ***"APS is a fast and reliable alternative to cascade impaction methods for particle size distribution measurements of most suspension formulations. Since APS has higher particle size resolution, it is more sensitive in detecting small changes in particle size distributions than ACI."***

Further investigations of pressurized MDIs (pMDIs) by Amina Alouache and co-workers from University of London and AstraZeneca echo similar observations on the accuracy and utility of the APS. The authors note that ***"the fine particle fraction value, $FPF_{4.7\mu m,}$ showed no statistical difference between the TSI System (APS) and the ACI."***

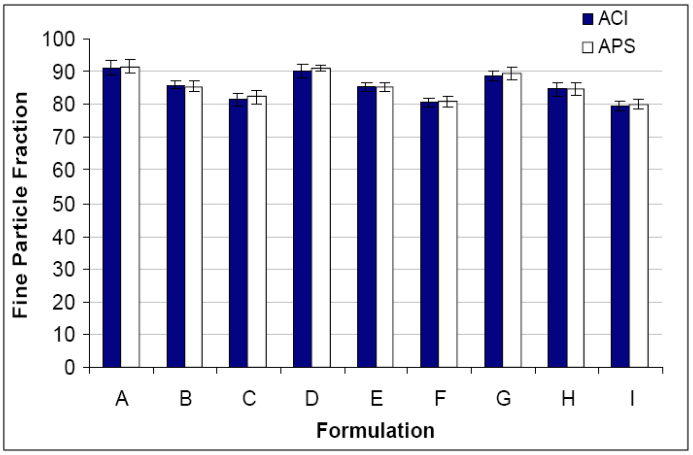

Figure 3. Data shown for pMDIs containing formoterol fumarate suspension formulations (n=3 S.D. (Figure adapted from Alouache et al., 2006)

Dry Powder Inhalers

DPI characterization is an emerging application where APS is finding increased use. M. Svensson from AstraZeneca has developed a method for analyzing doses from DPIs at optional flows utilizing the APS (Svensson et al., 2006). Their tests confirmed good correlation between APS and impactor measurements at various flow rates. ***"The APS proved 25 times faster than conventional impactor tests,"*** report the investigators.

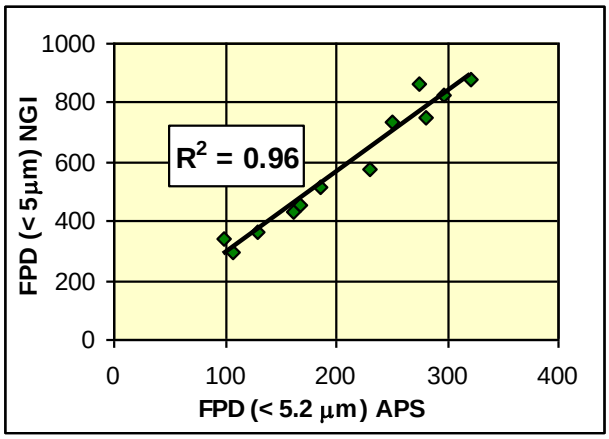

Figure 4. Fine particulate dose (FPD) evaluated at two different flows for 6 different powder formulations of pure drug. NGI stands for Next Generation Impactor (Figure adapted from Svensson et al. 2006)

Summary

Model 3321 APS spectrometer and Model 3306 impactor inlet are ideal development tools for rapid screening of spray and powder based inhalation aerosols. The time savings offered by these instruments facilitates improved efficiency of the product development processes, especially aiding the early formulation development stages that require large numbers of formulations and various operating parameters to be screened. The APS spectrometer provides robust measurements that correlate well with traditional cascade impactor methods.

References

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