

Dry powder inhalers (DPIs) are devices that deliver medications to the lungs to treat respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Although the compendial tests<sup>1</sup> for DPIs are based on cascade impactors, microscopic analysis provides useful information on both particle size and shape distributions of the powder products. Automated image analysis now facilitates quantitative particle size and shape distribution data that can prove valuable to both formulators and quality control efforts.

### Introduction

DPIs are an alternative to the aerosol based inhalers commonly called metered-dose inhaler (or MDI). The DPIs may require some procedure to allow a measured dose of powder to be ready for the patient to take. The medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices including the Inhalator, Spinhaler, Rotahaler, Turbuhaler, Accuhaler, the Diskus, and others. The dose that can be delivered is typically less than a few tens of milligrams in a single breath.

Some patients believe the DPI is easier to use because it is breath-activated, as opposed to MDIs where the patient activates the inhaler and inhales the medication at the same time. With a DPI the patient breathes in quickly to activate the flow of medication so the breath-activated discharge of medicine is always coordinated with the inhaling effort. Other benefits of DPIs over MDIs include the lack of a propellant and formulation stability. The disadvantages of DPIs include concern that insufficient patient inhalation flow rates may lead to reduced dose delivery, incomplete de-aggregation of the powder, and development/manufacturing costs.

The particle size distribution (PSD) of the delivered dose is more critical for inhalation aerosols than for most other conventional drug products. The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized as being in the range of 1 – 5  $\mu\text{m}$ . Many DPI formulations also include larger sized excipients that aid dispersion and powder flow.



Figure 1: Dry Powder Inhaler

### Particle Size Analysis

Pharmaceutical aerosols such as DPIs are unique compared to other drug delivery routes (such as tablets) in that the most important parameter for an inhalation product is usually the aerodynamic particle size distribution of the outgoing aerosol. The aerodynamic particle size distribution defines how an aerosol deposits during inhalation, and is influenced by the characteristics of powder particles such as shape and density, not solely by the size of the individual drug particles.

### Cascade Impactors

The aerodynamic particle size distribution is typically measured using a cascade impactor adsorption of nonionic polymer molecules to the surface of the dispersed phase (see Fig. 2). A multistage cascade impactor fractionates and collects particles of one or more drug components by aerodynamic diameter through serial multistage impactions.

Cascade impactors consist of a number of impactor stages connected in series with smaller and smaller cut-off diameters. The cut-off diameter in each stage depends on the air velocity and geometry of the stage (i.e. the distance from the nozzle to the impaction plate). Cascade impactors often have up to ten stages ranging from a cut-off diameter on the first stage of 10 – 30  $\mu\text{m}$  to a diameter  $\sim$  0.1  $\mu\text{m}$  or lower on the backup filter in the end.

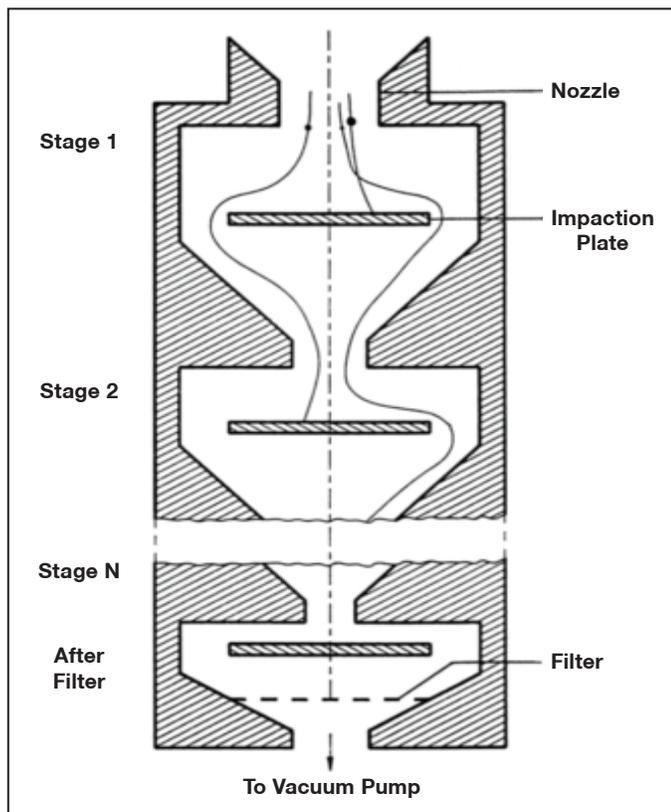


Figure 2: Cascade Impactor

Automated image analysis systems are now replacing manual microscopy in the pharmaceutical industry (see Figure 3). Since the data collection is completely automated, the number of particles analyzed can increase significantly to the point where the particle size and shape distributions can be quantified with confidence. In addition, modern algorithms can automatically separate touching particles, facilitating data collection and providing information on single particle characteristics.



Figure 3: PSA300 Image Analysis System

## Microscopic Evaluation

Although the preferred compendial test for the aerodynamic PSD of MDI's is the cascade impactor, USP <601><sup>1</sup> states that microscopy can be used to evaluate the number of large particles, agglomerates, and foreign particulates in the emissions of metered-dose inhalers. In addition, an FDA draft guidance document<sup>2</sup> suggests that the use of the microscope "has certain merits and, therefore, should be retained for release and stability purposes." Advantages of microscopic inspection include information on the following important characteristics:

- The presence of large particles
- Changes in morphology of the drug substance particle,
- Extent of agglomeration
- Crystal growth
- Presence of foreign particulate matter

Since the crystalline form of the drug substance can affect the bioavailability, performance, stability, or other properties of the drug product, the FDA guidance document recommends microscopic evaluation or other appropriate methods to control and monitor the morphic form if changes are observed on stability. Microscopic analysis can be used throughout development and manufacturing, but may be most useful for early characterization of drug substance and to evaluate crystal growth and agglomeration during temp cycling studies. This test may also be useful later during stability and release testing.

## Experimental

A bronchodilator DPI containing salmeterol and fluticasone was examined using the PSA300 image analysis system. The device was actuated and the powder dose was tapped into the nozzle of the Disperser Unit. The Disperser Unit operates by placing the powder into the bottom of a nozzle, which is locked into place within a chamber containing microscope slides. A vacuum is pulled and then released, provided energy to disperse the particles which fall onto the microscope slides. The slides are then loaded into the PSA300 for inspection.

Next a routine was created within the PSA300 software that was optimized for the application. Important aspects of the measurement controlled by the routine included the magnification, light intensity, portion of the slide inspected, threshold setting, particle separation approach and sensitivity, and parameters assigned to each particle. This routine was then applied to the slide and the results shown in Table 1 were generated. Note size is reported as circle diameter vs. spherical volume in  $\mu\text{m}$ . Both roundness and aspect ratio (dimensionless) are reported on a count basis. The particle size distribution is shown in Figure 4.

	Size	Roundness	Aspect ratio
<b>D10:</b>	2.4	0.48	1.15
<b>D50:</b>	4.8	0.68	1.37
<b>D90:</b>	8.6	0.83	1.86
<b>Minimum:</b>	0.6	0.24	1.05
<b>Maximum:</b>	15.7	0.93	3.68
<b>Mean:</b>	5.49	0.667	1.46

Table 1: DPI 500x Results

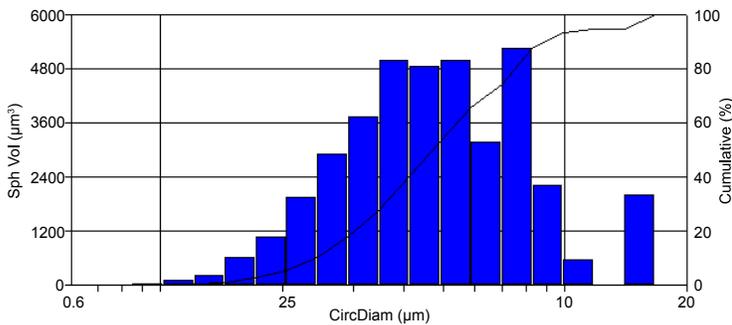


Figure 4: DPI 500x Particle Size Distribution

After generating the data above at 500x, the same sample was measured using the 100x objective and 80% of the total slide area was inspected to look for large particles and/or foreign particulates. The particle size and shape information for this result does not include the smaller particles, but switching to the 100x objective greatly increases the analysis time for inspecting a larger area. The results for this analysis are shown in Table 2. The particle size distribution is shown in Figure 5. The result calculation basis is the same as described for the 500x experiment.

	Size	Roundness	Aspect ratio
<b>D10:</b>	85	0.51	1.07
<b>D50:</b>	118	0.75	1.3
<b>D90:</b>	159.6	0.92	1.79
<b>Minimum:</b>	3.2	0.15	1.06
<b>Maximum:</b>	168.3	0.93	4.88
<b>Mean:</b>	121	0.729	1.39

Table 2: DPI 100x Results Slide 1

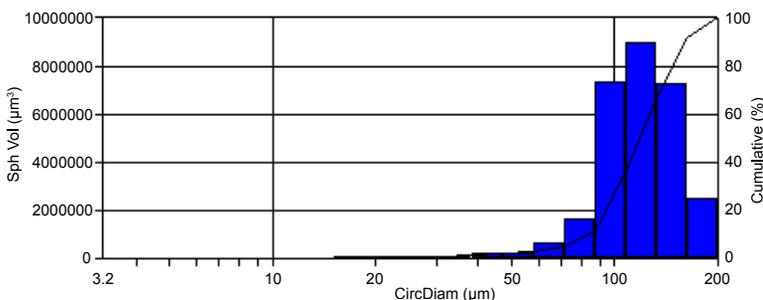


Figure 5: DPI 100x Particle Size Distribution

Due to the dramatic shift in the 100x result, the same experiment was repeated in order to test reproducibility. The results for the second slide are shown in Table 3.

	Size	Roundness	Aspect ratio
<b>D10:</b>	40	0.54	1.07
<b>D50:</b>	113.1	0.77	1.27
<b>D90:</b>	155.2	0.92	1.73
<b>Minimum:</b>	3.2	0.12	1.05
<b>Maximum:</b>	162.2	0.93	4.8
<b>Mean:</b>	108.3	0.743	1.36

Table 3: DPI 100x Results Slide 2

## Discussion

The 500x results represent the most accurate information for the particle size and shape distributions of the sample. Switching to the 100x objective provided quick inspection of many more fields, and therefore particles. In this example the 100x measurement looked at 600 fields and inspected 7200 particles. This result reported that the largest particle inspected was 168 µm. The largest particles analyzed during the measurement were manually viewed post inspection and several representative images were saved (see example in Figures 6 and 7).

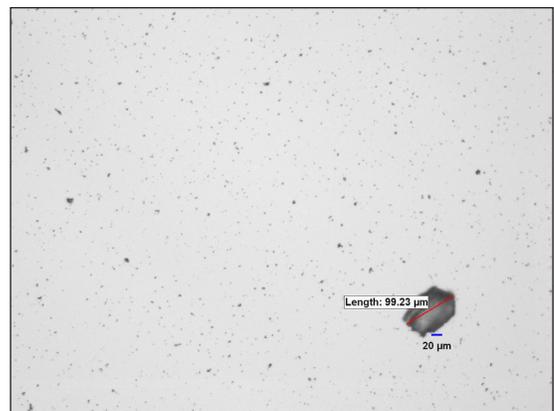


Figure 6: Large Particle 1 from DPI

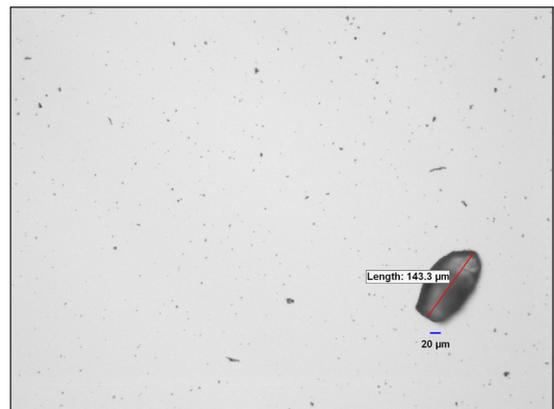


Figure 7: Large Particle 2 from DPI

This process is facilitated at the end of the measurement through a data browser that sorts all inspected particles on any chosen criteria. The operator then clicks on any particle in the browser and the stage moves the slide to that particle for inspection, rejection, or saving of the individual image. Large foreign particles may possibly be collected for further analysis using this technique.

## Conclusion

The PSA300 provided the complete particle size and shape distribution characterization of a sample collected from a DPI. This data may be helpful for DPI formulation, manufacturing control, trouble shooting, and many other possible applications.

## References:

1. USP<601> Metered Dose Inhalers and Powder Inhalers
2. Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), October 1998, [www.fda.gov/cder/guidance/2180dft.pdf](http://www.fda.gov/cder/guidance/2180dft.pdf)