HORIBA Scientific

Application Note

Particle Characterization of Metered-Dose Inhalers

AN169

Metered-dose inhalers (MDIs) are devices that deliver a specific quantity of drug to the lungs. The size and shape of the micronized drug greatly influence the deposition profile in the lungs of the patient. Although the compendial tests for MDIs are based on cascade impactors, microscopic analysis is recommended by regulatory guidance documents and delivers important information. Automated image analysis now facilitates quantitative particle size and shape distribution data that can prove valuable to both formulators and quality control efforts.

Introduction

An MDI typically delivers a specific dose of a micronized drug by supplying a short burst of aerosolized medicine that is inhaled by the patient. It is commonly used to treat respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD). The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of those two.

The MDI device (see Figure 1) consists of a canister, and actuator, and sometimes a spacer. The canister itself consists of a metering dose valve with an actuating stem. The formulation resides within the canister and is made up of the drug, a liquefied gas propellant, and often stabilizing excipients. The actuator contains the mating discharge nozzle and generally includes a dust cap to prevent contamination

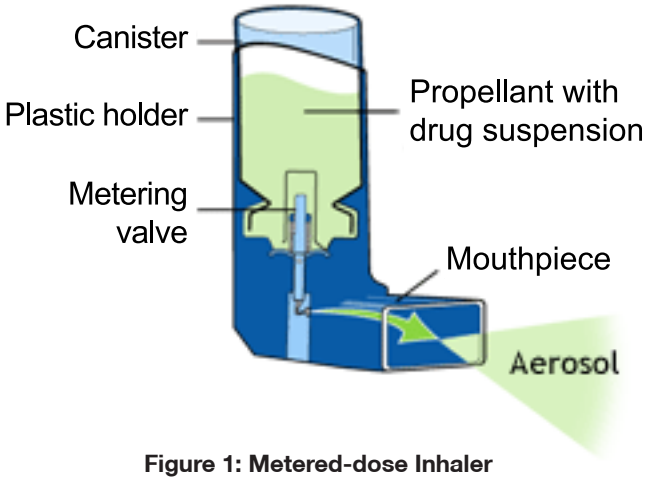

Figure 1: Metered-dose Inhaler

Actuation of the device releases a single metered dose of liquid propellant that contains the medication. The volatile propellant breaks up into droplets which then evaporate, creating an aerosol containing micronized drug that is inhaled into the lungs.

The particle size distribution (PSD) of the delivered dose is more critical for inhalation aerosols than for most other conventional drug products. The PSD is dependent on the drug formulation, the valve, and the mouthpiece. The optimum aerodynamic particle size distribution for most inhalation aerosols has generally been recognized as being in the range of 1 – 5 µm.

Particle Size Analysis

MDIs 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 the spray of the drug product, not solely by the size of the individual drug particles initially suspended in the formulation.

Cascade Impactors

The aerodynamic particle size distribution is typically measured using a cascade impactor (see Figure 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 mm to a diameter ~ 0.1 mm or lower on the backup filter in the end.

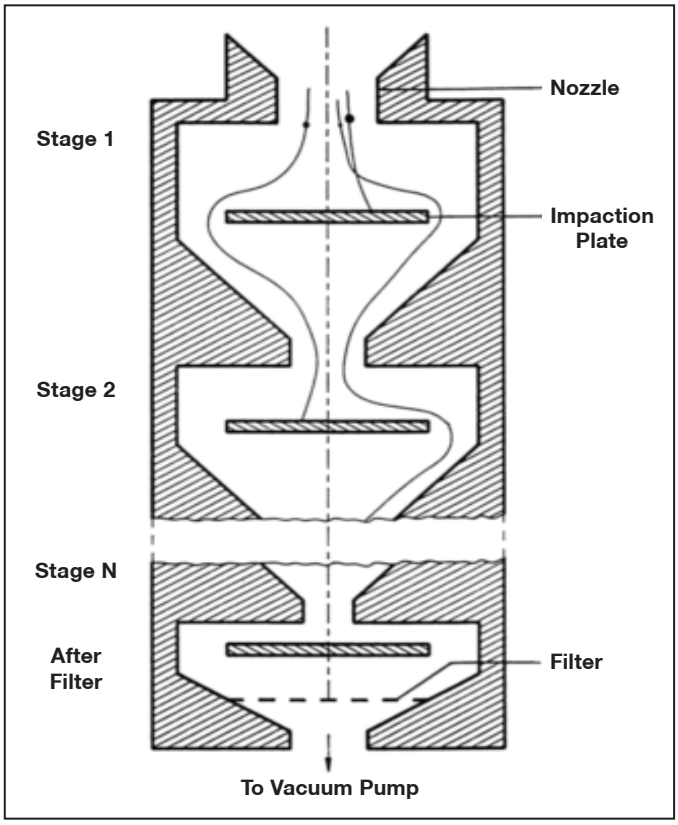

Figure 2: Cascade Impactor

Microscopic Evaluation

Although the preferred compendial test for the aerodynamic PSD of MDI's is the cascade impactor, USP <601>[1] 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[2] 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.

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 high statistical 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

Experimental

A bronchodilator MDI was examined using the PSA300 image analysis system. Traditional industry guidelines suggest that the MDI be actuated onto a clean, dry slide held 5 cm from the device, perpendicular to the direction of the spray. The slide was then examined using the 500x magnification objective in the PSA300. An initial study investigated the effect of the distance between the MDI device and microscope slide. Figure 4 below shows a typical area of concentrated particles when the device was actuated too close to the slide (~ 5 cm).

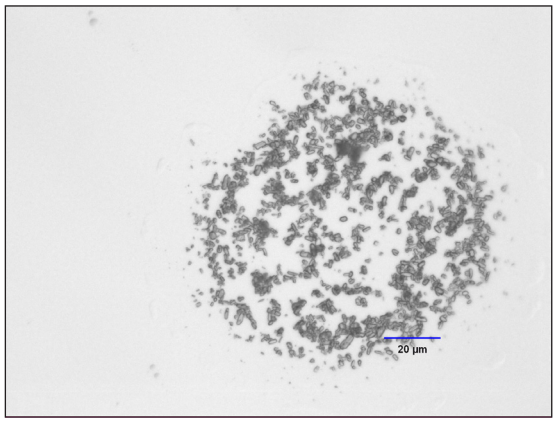

Figure 4: Concentrated Particles

The MDI was then placed ~ 15 cm from the slide and actuated twice. Figure 5 shows typical particle placement on the slide after this preferred optimum distance was determined.

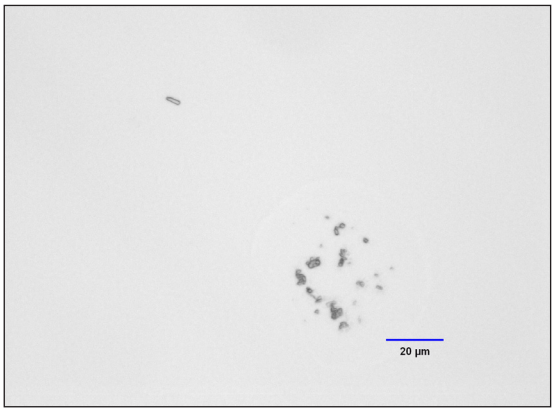

Figure 5: Dispersed Particles

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 µm. Both roundness and aspect ratio (dimensionless and defined as length over breadth) are reported on a count basis. The particle size distribution is shown in Figure 6.

	Size	Roundness	Aspect ratio
D10:	2.3	0.43	1.19
D50:	3.9	0.6	1.51
D90:	6.4	0.78	2.05
Minimum:	0.6	0.27	1.07
Maximum:	8	0.93	3.27
Mean:	4.21	0.61	1.58

Table 1: 500x Results

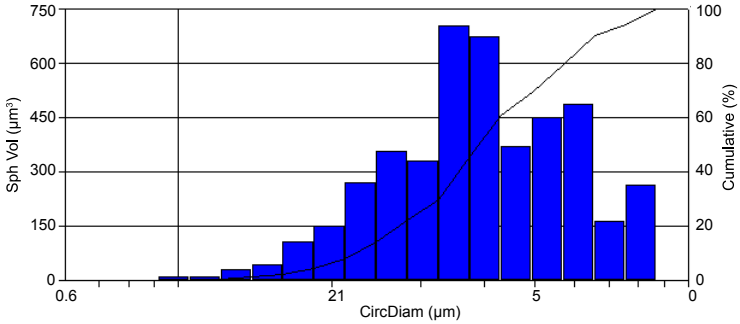

Figure 6: MDI 500x Particle Size Distribution

After generating the previous data 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 decreases 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 7. The result calculation basis is the same as described for the 500x experiment.

	Size	Roundness	Aspect ratio
D10:	5.3	0.47	1.07
D50:	10.7	0.74	1.3
D90:	28.1	0.92	1.8
Minimum:	3.2	0.13	1.05
Maximum:	46.2	0.93	5.39
Mean:	13.5	0.709	1.39

Table 2: 100x Results

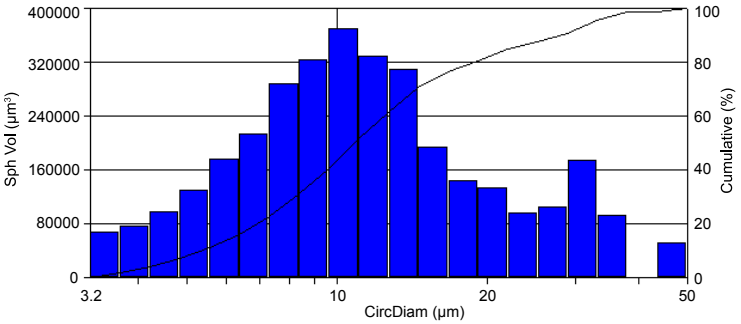

Figure 7: MDI 100x Particle Size Distribution

Discussion

The 500x results represent the most accurate information for both 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 480 fields and inspected 16,169 particles. This result reported that the largest particle inspected was 46.2 µm. The largest particles analyzed during the measurement were manually viewed post inspection and several representative images were saved (see example in Figure 8 where a 20 µm particle appears to be a single particle, not an agglomerate).

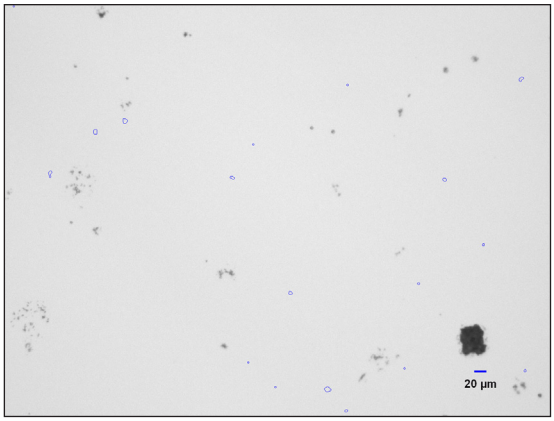

Figure 8: Large Particle from MDI

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

Image analysis supports the particle sizing information delivered by cascade impactors and other techniques, and automating the image analysis process greatly reduces the time and effort spent validating results. The PSA300 provided the complete particle size and shape distribution characterization of a sample collected from an MDI in a matter of minutes with a single, push-button routine. This information may be helpful for MDI 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