A novel aerodynamic sizing method for pharmaceutical aerosols using image-based analysis of settling velocities

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Abstract

This article discusses a novel method to estimate aerodynamic particle size distributions (APSDs) of pharmaceutical aerosols through direct measurement of particle settling velocities using image-based analysis and particle tracking techniques. This simple, optical method provides accurate and fast measurements (approximately 1 minute) with few sources of bias due to specific device design choices or operating conditions. A proof-of-concept for the method is demonstrated by measuring APSDs for widely available commercial dry powder inhalers (DPIs), then comparing the results with previously published data from cascade impactors (CIs) and the Aerodynamic Particle Sizer (APS).

Introduction

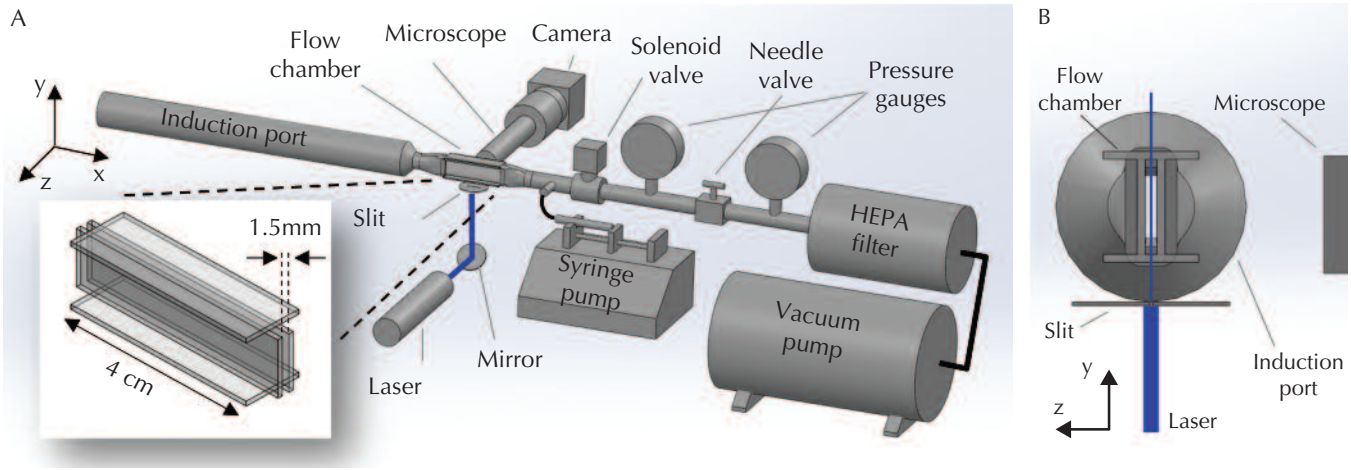
Measurements of aerodynamic particle size distributions (APSDs) from orally inhaled products (OIPs) are important for estimating the inhaled drug dose and are a key component for development and validation of drug/inhaler combinations. Currently, the only APSD estimation method approved for regulatory purposes in both US and European pharmacopeias[1, 2] is based on the collection of particle fractions using a cascade impactor (CI) or a liquid impinger, followed by chemical analysis (e.g., high performance liquid chromatography) of drug weight within these fractions. This approach has several advantages including estimation of aerodynamic (rather than geometrical) diameters, chemical specificity that distinguishes drug-containing particles from excipient particles and full sampling of the whole dose rather than a limited sample. Despite such advantages, CI-based analysis remains not only relatively expensive but also very time-consuming. Thus, this method is often impractical for applications where high throughput measurements are important, such as product development and, particularly, extensive stability studies. Furthermore, CI-based results are known to yield pronounced variability across different CI designs.[3, 4] Notably, one anticipates approximately a 30% difference in the measured mass median aerodynamic diameter (MMAD) from a Next Generation Impactor™ (NGI) (TSI, Incorporated, St. Paul, MN, US) compared to an Andersen Cascade Impactor (ACI).[4] Such large differences are somewhat surprising in light of the high reproducibility of each single impactor (i.e., generally around 2-3% in MMAD estimation). Although an in-depth discussion detailing the sources of variability in OIP characterization is beyond the scope of the present article and has been discussed elsewhere[3, 5] it should be emphasized that CI-based methods are extremely sensitive to small changes in device design (e.g., nozzle diameter) and operation conditions (e.g., flow rate).

The search for faster OIP characterization methods has led to the adaptation of several real-time techniques for this purpose.[6] However, among the available methods, the Aerodynamic Particle Sizer® (APS) (TSI Incorporated, St. Paul, MN, US) is the only apparatus that directly measures aerodynamic particle diameters.[7] Despite its advantages, the APS remains a relatively complicated device that requires complex optics, in conjunction with sample dilution, to avoid particle coincidence errors. Other sources of bias, such as droplet distortion and phantom particles, should also be considered.[5] Furthermore, such high-end devices are relatively costly and often remain beyond the reach of early, cash-strapped, startup companies that are in the initial phases of developing new inhalation devices.

This article presents a simple, fast (i.e., approximately 1 minute per measurement) and cost-effective method

Figure 1

Schematic illustration of (A) the prototype system with an expanded view of the flow chamber design (inset) and (B) a cross-section through the flow chamber



for obtaining APSD measurements from OIPs based on direct estimation of particle settling velocities using image analysis. While conceptually similar methods have been previously reported for determining settling velocities of particles in water[8, 9] or air,[10] this novel method is designed specifically for OIP characterization and includes means for particle sampling and simultaneous analysis of multiple particles. The simple principle of operation, which was recently patented (#PCT/IL2016/050979), offers few sources of variability, suggesting that this method has the potential for giving reproducible results across different designs and manufacturers as well as machine operators. Furthermore, the system is designed to sample aerosols from the inhaler with no need for dilution, even for the densest aerosols, thereby circumventing any dilution-related measurement biases.

As a proof-of-concept, APSDs have been obtained from two widely used commercial dry powder inhalers (DPIs). These measurements are compared to previously published measurements from CIs and the APS. In addition, the article discusses directions for future work and foreseeable improvements for the current design, in anticipation of broadening its applicability.

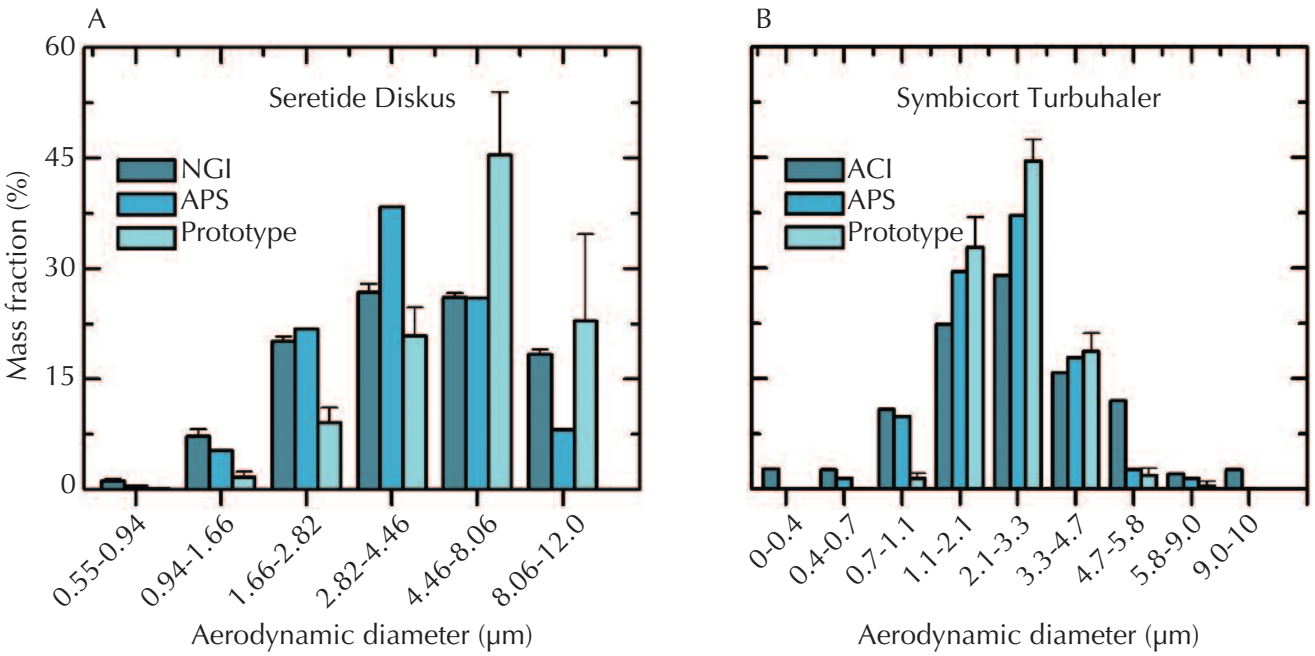
Design

Figure 1 shows a schematic, computer-aided (CAD) illustration of the prototype design. The following is a brief description of the measurement steps. To begin, a flow meter is attached to the induction port, the vacuum pump is turned on and the flow rate is adjusted, using the needle valve, to the desired rate, based on the specific inhaler (e.g., 60 L/min). Two pressure gauges, located on each side of the needle valve, are used to ensure limiting flow conditions through the valve (i.e., a pressure ratio larger than two). Note that the induction port used in the current prototype is made of a straight tube (length 22 cm, inner diameter 21.5 mm) rather than an L-shaped throat, in order to maximize the number of measured particles. Next, an inhaler is attached to the induction port and primed according to the manufacturer's instructions. An experiment is initiated when the solenoid valve is opened through a remote, computer-controlled signal for approximately 0.1 seconds, drawing the particles into the transparent flow chamber (Figure 1A inset). The rectangular flow chamber is comprised of four glass plates, which are plated with ITO (a conductive and transparent material) to reduce electrostatic particle deposition. Once the solenoid valve is shut and the aerosol bolus reaches a near-stop, the particles within the chamber are imaged at a horizontal angle, using a 4X microscope and a fast camera (Figure 1, parts A and B) operating at 166 frames per second (fps) to create a set of 30 consecutive frames.

Following the experiment, automatic image analysis, based on particle tracking techniques, is used to determine the aerodynamic diameter of the imaged particles, based on their settling velocities. These measurements are converted to a mass-weighted size distribution by assuming a spherical shape of the particles and a homogenous density that may give rise to sources of error in ensuing measurements when compared to other techniques. During imaging, the particles inside the flow chamber are illuminated using a thin laser sheet created by a laser diode (450 nm, 100 mW) and a 100 µm wide optical slit (Figure 1B). Using the Fresnel diffraction equation for calculation, the intensity of light inside the camera's field of view (FoV) is below 10% of the maximal intensity at a distance of 63 µm from the mid-plane of the laser sheet. Therefore, only particles that are in the vicinity of the imaging plane of the microscope are illuminated (Figure 1B) while stray light from out-of-focus particles is attenuated. Note that the slender design of the flow chamber (inner

Figure 2

APSD measurements obtained using the prototype device and published data from CI and APS measurements for two commercial DPIs (see text for references)



dimensions: 1.5 mm x 12 mm, see the inset in Figure 1) assists in damping residual flows. To increase the total number of imaged particles per experiment, the syringe pump then withdraws a small amount of aerosol that replaces the particles within the chamber with a new set of particles that have not yet been imaged. In this manner, at least three different sets of particles can be examined from a single aerosol sample. After the measurement, the solenoid valve opens for approximately 10 seconds to clean the system and the particles are collected by the HEPA filter (Figure 1A).

Proof-of-concept experiments

The results of APSD measurements from two commercial drug/inhaler combinations are presented in Figure 2 alongside published benchmark experiments obtained using a CI or the APS. The corresponding MMADs and geometric standard deviations (GSDs) are summarized in Table 1 for quick comparison.

While the APSD measurements obtained with the new system for a Symbicort® Turbuhaler® (AstraZeneca, Cambridge, UK) inhaler agree very well with results from the Andersen Cascade Impactor (ACI)[11] and the APS,[12] an overestimation of MMAD is observed for measurements from a Seretide® Diskus® (GlaxoSmithKline, Brentford, UK) compared to the NGI[13] and the APS.[12] Note in particular the higher estimation of particle density in the size range of 4.46-8.06 µm (Figure 2A). Nevertheless, such discrepancies do not exceed differences previously reported between APS and CI measurements.[3]

While discrepancies between these measurements and the literature may result from biases associated with the traditional methods, sources of variability related to limitations of preliminary experiments with the system should also be considered. For example, the use of a straight tube as an induction port, rather than an L-shaped throat, can lead to biased results because the bent geometry is known to alter particle size distributions through particle deposition and agglomerate breakup.[14] In addition, different batches of inhalers have been used, compared to published data. Another source of bias in these measurements may stem from a lower detection rate for smaller particles, a limitation that may be overcome by introducing a proper calibration scheme by measuring monodispersed particles of known size and density. Note also the higher variability in the measurements for larger particles (compare Figures 1A and 1B). This may result from the lower number of particles measured for larger particles compared to smaller ones. For example, only 405 particles were measured, on average, in a single measurement for a Seretide Diskus compared to 2,870 particles for a Symbicort Turbuhaler.

Obtaining more accurate measurements across the larger particle range would require increasing the number of measured particles, for example, by adding a second imaging system with a larger FoV. Finally, one should recall that the initial assumptions of spherical particles and constant density may add to observed discrepancies between these measurements and CI-based data.

Despite these limitations, promising results have been obtained using this initial prototype. Specifically, aerodynamic particle size measurements with the device seem to be most accurate in the particle size range of 1-5 µm. It is expected these measurements

Table 1

MMAD and GSD measurements for two drug/DPI combinations, compared to data from the literature

Inhaler	Flow Rate (L/min)	Mass Median Aerodynamic Diameter (MMAD) (µm)			Geometric Standard Deviation (GSD)		
		Cascade Impactor	Time of Flight (ToF)	Prototype	Cascade Impactor	Time of Flight (ToF)	Prototype
Symbicort® Turbuhaler®	60	2.6	2.4	2.5 ± 0.1 (n = 9)	2.1	1.7	1.5 ± 0.03 (n = 9)
Seretide® Diskus®	60	4.1 ± 0.1	3.8	6.0 ± 0.7 (n = 9)	2.0 ± 0.03	1.8	1.7 ± 0.09 (n = 9)

will become more accurate and span a larger size range as device development continues.

Conclusions and future work

Although CI-based analysis stands as the only method currently approved for regulatory purposes, the labor times and high costs, as well as relatively large measurement biases, call for faster and more reliable methods for APSD estimation. Such methods, despite lack of chemical specificity, may prove valuable for high throughput screening of devices and drugs during product development and serve as a complementary method for validation of existing measurement methods.

For the first time, a proof-of-concept study has shown the feasibility of obtaining meaningful aerosol measurements from DPIs, in approximately 1 minute, using direct estimation of settling velocities with automatic image analysis. While only DPIs were used in this study, the method can, in principle, be adapted for pressurized metered dose inhalers (pDMIs) as well as nebulizers by preventing droplet evaporation through humidification or cooling of the system.

With further development, this method has the potential to become a standard reference replacing or complementing current OIP characterization methods because this simple measurement method is inherently tolerant to minor changes in the design of the measurement system or in its operating conditions. In addition, the particle-by-particle measurement approach may prove useful for measuring very low drug doses (e.g., 5 or 10 mg). Furthermore, due to its simplicity, the system may serve as a cost-effective alternative to current OIP characterization techniques and even be assembled in a research laboratory setup from off-the-shelf materials.

Future work includes further verification of the device capabilities, expanding its abilities towards measurement from various inhalation devices, introducing a calibration scheme to correct for possible biases due to size-dependent detection rates and increasing the number of measured particles per measurement in order to increase the accuracy and the size range.

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