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Particle sizing of pharmaceutical aerosols via direct imaging of particle settling velocities

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Abstract

We present a novel method for characterizing in near real-time the aerodynamic particle size distributions from pharmaceutical inhalers. The proposed method is based on direct imaging of airborne particles followed by a particle-by-particle measurement of settling velocities using image analysis and particle tracking algorithms. Due to the simplicity of the principle of operation, this method has the potential of circumventing potential biases of current real-time particle analyzers (e.g. Time of Flight analysis), while offering a cost effective solution. The simple device can also be constructed in laboratory settings from off-the-shelf materials for research purposes. To demonstrate the feasibility and robustness of the measurement technique, we have conducted benchmark experiments whereby aerodynamic particle size distributions are obtained from several commercially-available dry powder inhalers (DPIs). Our measurements yield size distributions (i.e. MMAD and GSD) that are closely in line with those obtained from Time of Flight analysis and cascade impactors suggesting that our imaging-based method may embody an attractive methodology for rapid inhaler testing and characterization. In a final step, we discuss some of the ongoing limitations of the current prototype and conceivable routes for improving the technique.

Keywords

Particle sizing; Image analysis; Aerodynamic size; Particle tracking; Settling velocity; Pharmaceutical aerosols; Dry powder inhalers (PDI)

1 Introduction

Aerodynamic particle size distributions of pharmaceutical aerosols are important for determining the inhaled dose from medical inhalers and nebulizers as well as the drug's spatial distribution within the lungs upon deposition. For such reason, an accurate characterization of aerodynamic size distributions is essential in the development, approval and validation of inhaled drug formulations and inhalation devices (European Pharmacopeia, 2017; US Pharmacopeia, 2016). To date, cascade impactor (CI) analysis is the only approved method for aerodynamic particle sizing from inhalers and nebulizers. This method is performed by collecting several particle size fractions from an inhalation device using a CI,

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and subsequently analyzing their content using a chemical assay (e.g. HPLC). Yet, such state-of-the-art measurements are relatively time consuming, expensive, and prone to many sources of variability (Hickey and Swift, 2011), which may lead to ~30% difference in the measured mass median aerodynamic diameter (MMAD) between different CI designs (Taki et al., 2010).

Such disadvantages have led to the adaptation of several real-time particle sizing methods for providing fast particle measurements from inhalers and nebulizers (Mitchell et al., 2011). These methods include Time of Flight (ToF) analysis (Stein et al., 2003), electrical single-particle aerodynamic relaxation time (E-SPART) analysis (Ali, 2010), Single-Particle Light Scattering (SPLS) (Gebhart, 2001) laser diffractometry (LD) (Mitchell et al., 2006), Electrical Low Pressure Impactor (ELPI) (Glover and Chan, 2004), and single particle aerosol mass spectrometry (SPAMS) (Morrical et al., 2015). Among these methods, ToF, E-SPART, ELPI and SPAMS are used to measure aerodynamic particle size, while SPLS and LD essentially yield a geometric particle size. In addition, LD is the only method to yield a mass-weighted size distribution, while the other methods measure a count-weighted distribution that can be subsequently translated to a mass distribution upon assuming effective density and shape factors. Finally, E-SPART and ELPI are the only methods to measure particle electrical charge distributions. Table 1 summarizes several of the attributes of the methods introduced above. It is important to note, however, that none of the fast methods alluded can replace CI measurements as a “gold standard” for regulation. This is due foremost to the lack of chemical specificity, which is necessary for measuring the amount of drug in each particle size fraction. In addition, only CIs capture the whole emitted mass. While SPAMS does have the capability of providing on-line chemical specific particle measurement, and could in principle replace CI measurements, it has yet to mature into a commercial technology, and the extremely high costs of the system may impede its practicality for this purpose (Morrical et al., 2015). The fast methods are therefore mainly intended to enable high throughput measurements that may be essential in product development stages and for extensive stability studies.

In the present work, we report a simple and fast method for the quantitative characterization of aerodynamic particle size distributions of pharmaceutical aerosols based on direct time-resolved observation of particle settling velocities similar to particle tracking velocimetry (PTV). Namely, the measurement of a particle's settling velocity allows an accurate estimation of its aerodynamic diameter since the aerodynamic diameter is defined as the diameter of a sphere with a density of 1000 kg/m³ having the same settling velocity as the measured particle. In contrast to previous efforts which include sedimentation cells (Stahlhofen et al., 1975), the present measurement technique is specifically designed to allow direct sampling from medical inhalers or nebulizers without any dilution. Moreover, the horizontal design of the measurement chamber, where streamwise flow direction is orthogonal to gravity, allows accurate measurements without the need to avoid streamwise convection currents. Using this prototype, we demonstrate the feasibility of the system as a measurement tool for pharmaceutical aerosols by measuring particle size distributions from several commercial dry powder inhalers (DPIs) and comparing the results to ToF analysis performed on the same inhalers, and to available data from the literature obtained using CIs.

In a final step, we discuss some of the limitations of the proposed method and identify foreseeable opportunities to improve and expand the capabilities of the current prototype.

2 Methods

2.1 Rationale and overview of the prototype

Direct visualization of particles in water (Chase, 1979; Dearnaley, 1996) or air (Stahlhofen et al., 1975) for the purpose of determining particle aerodynamic diameter are typically conducted in a vertical tube where drift flows are minimized. Despite the simplicity of such approaches, several challenges must be addressed before a similar method can be used for determining aerodynamic sizes of particles emitted from medical inhalation devices. To begin, the aerosol should be extracted from the inhaler or nebulizer at a desired flow rate (i.e. typically in the range of 15 to 60 L/min); next, a representative sample of particles should be directed into a sedimentation chamber where drift flows are minimized; third, the number of measured particles should be adequate for reconstructing accurate size distributions; and finally, in light of the high aerosol concentrations typical of therapeutic aerosols, noise due to out-of-focus particles in the field of view (FoV) should be reduced during direct imaging.

The prototype described here is constructed from a single air path leading from the inhaler into a flow control unit (Fig. 1a). The aerosol is first extracted from the inhalation device at a predefined flow rate and directed into a rectangular flow chamber constructed of glass (Fig. 1a, inset). In a subsequent step, the flow rate is reduced to allow direct visualization of single particles. In contrast to previous chamber designs (Chase, 1979; Dearnaley, 1996; Stahlhofen et al., 1975), the direction of flow in the present configuration is horizontal rather than vertical. Thus, the settling velocity of the particles, measured as the vertical component of particle velocity, is not affected by flow in the streamwise (horizontal) direction. This design greatly simplifies the measurement method since drift flows along the principle streamwise flow direction are generally more pronounced compared to flows in the perpendicular direction. Next, the particles are imaged in dark field through the glass slates composing the flow chamber while a laser light sheet illuminates the particles at a right angle to the camera's viewing direction (Fig. 1b). Since only a narrow ($\sim 100\ \mu\text{m}$) section of the aerosol close to the imaging plane is illuminated (see details below), light scattering from out-of-focus particles is minimized. Finally, image analysis is used to track single particles and determine their aerodynamic size based on their settling velocity. The whole procedure was performed automatically, where a single Matlab script was used both for controlling the system (i.e. the syringe pump, the solenoid valve and the camera) and for executing image analysis. With this setup, one measurement can be performed in < 1 min. Thus, the current system allows fast measurements of aerodynamic diameters through particle-by-particle inspection, similar to ToF analysis (see Table 1). Furthermore, the simple sampling technique of our method circumvents much of the possible biases of ToF analysis including those related to sample dilution, non-Stokesian particle Reynolds numbers, droplet distortion, particle coincidence and phantom particles (Kulkarni et al., 2011).

2.2 Prototype design

2.2.1 Induction port—Unlike other existing devices for the characterization of pharmaceutical aerosols, which include a throat-like angled induction port, we opted here instead for a straight aluminum tube (length 22 cm, inner diameter 21.5 mm) to connect the inhaler with the flow chamber (Fig. 1a). While the geometry of the induction port is known to have a significant influence on particle size distributions due to particle deposition and agglomerate breakup (Dolovich and Rhem, 1998; Nichols et al., 2013), we chose in a first step to use a straight tube in order to maximize the amount of particles imaged inside the prototype. Nevertheless, we closely matched the diameter and total length of the tube to the standard L-shaped induction port (European Pharmacopeia, 2008). A leak tight connection between the inhalation device and the induction port was achieved using adhesive putty.

2.2.2 Flow chamber—The rectangular flow chamber (Figs. 1a,b and 2) was constructed from 1 mm thick glass plates coated from one side with indium tin oxide (ITO) for reducing electrostatic particle deposition. The plates were connected using epoxy adhesive with the ITO covered side facing inwards to create a 4 cm long chamber with inner dimensions of 1.5 mm × 12 mm. This narrow design reduces significantly residual flows in the direction orthogonal to the initial streamwise flow, thus allowing accurate measurements of settling velocity by measuring the vertical component of particle motion, as mentioned earlier. Indeed, while developing the system, we observed that chambers having larger widths often resulted in a vortex swirling around the axis of the chamber rather than a near-stop of the flow. The width of the chamber was therefore reduced as much as possible to suppress vortex formation without interfering with the light sheet (see Camera and illumination system section below) and without increasing the flow resistance above that of the needle valve (see Flow control system section below). A 3.5 cm long PVC tube with an inner diameter of 8 mm was used to connect the flow chamber with the induction port, and a similar tube was used to connect chamber to the flow control system. To create a gradual transition from the circular tube to the rectangular chamber the tubes were reshaped by heating and stretching the tubes' edges. The tubes were then connected and sealed to the glass chamber using epoxy adhesive.

2.2.3 Flow control system—To ensure that flow conditions are as close as possible to those used in CI measurements, we designed the flow control system in close accordance with standard pharmacopeia guidelines for cascade impactor operation (European Pharmacopeia, 2008; US Pharmacopeia, 2016), notwithstanding some minor modifications (see Fig. 1c). Namely, a vacuum pump (Gast, model 1423) was connected to the flow chamber outlet through a needle valve with a maximal orifice size of 3/8" for adjusting flow rate. Two differential pressure gauges (– 1 to 0 bar), located upstream and downstream of the needle valve, were used to ensure limiting flow conditions (i.e. a pressure ratio of more than two). A two way solenoid valve (Baccara, Gem-B-33, orifice size 3/8", 24 V DC 10 W) was used to automatically open and close the airflow through the flow chamber, and computer controlled via Matlab using a 5 V analog data output from a data acquisition card (USB 6211, National Instruments), which was amplified using a 24 V DC power supply and a Mofset module (Tinkercat T010020). In contrast to flow control units used in cascade impactors, the solenoid valve was located upstream of the needle valve to allow faster

changes of velocities inside the flow chamber. In addition, an in line HEPA filtration unit (Whatman, Hepa-Cap 150) collected the microparticles from the aerosol before entering the vacuum pump, and a syringe pump was connected between the flow chamber and the solenoid valve for controlling slower flow maneuvers (see Measurement procedure section below). This syringe pump was automatically controlled using a Matlab code and a USB connection.

2.2.4 Camera and illumination system—A USB-3 camera (IDS, UI-3060CP-M-GL Rev.2) featuring a resolution of 1936×1216 pixels and a maximal frame rate of 166 frames per second was mounted with a $4 \times$ video lens (Infinity, Infinistix), thus resulting in a FoV of $\sim 1.8 \text{ mm} \times 2.5 \text{ mm}$ and placed horizontally near the flow chamber (see Fig. 1b). The camera was connected to a computer through a USB-3 connection and directly controlled from a custom Matlab code using a .NET interface.

A blue laser diode (Civillaser, 450 nm, 100 mW, dot module) with an adjustable focusing lens was set to a focal length of 65 cm and used to illuminate the flow chamber from the bottom by reflecting the light from a slanted mirror. The distance from the laser diode to the flow chamber was 25 cm where the width of the beam was $\sim 2 \text{ mm}$. To reduce noise due to reflection from out-of-focus particles, an optical slit $100 \mu\text{m}$ in width was placed at a distance of 5 mm from the bottom side of the flow chamber (and 10.6 mm from the center of the FoV of the camera), thus creating a thin laser sheet by reducing the width of the beam in the direction parallel to the viewing angle (Fig. 1b). Using the Fresnel diffraction equation we calculated that within the camera's FoV the intensity of light inside the chamber was below 10% of the maximal intensity at a distance of $63 \mu\text{m}$ from the mid-plane of the laser sheet. This is shown in Fig. 3, highlighting the intensity profile along the camera's line of sight (i.e. z -direction) for three locations along the direction of the light beam, y , with the assumption of an infinitely long slit (see coordinate system in Fig. 1b). These locations correspond to the bottom ($y = 0.94 \text{ cm}$), middle ($y = 1.06 \text{ cm}$) and top ($y = 1.18 \text{ cm}$) of the camera's FoV, where $y = 0$ corresponds to the position of the slit (see Fig. 1b). Here, the effects of the bottom slate of the flow chamber are neglected due to the low incident angles. However, light scattering from particles deposited on the bottom of the flow chamber and airborne particles as well as light reflected from the top slate of the chamber all contribute to undesirable background light in our system.

2.2.5 Measurement procedure—Prior to conducting the measurements, a mass flow-meter (TSI, 4043) was connected at the flow inlet (instead of the inhaler), and flow rate through the prototype was adjusted using the needle valve to 55–65 L/min depending on the individual inhaler. Next, the inhaler was primed according to the manufacturer's instructions and attached to the flow inlet using adhesive putty to achieve an air-tight connection; the laser and vacuum pump were turned on and the room was darkened. Particle sampling and measurement were then automatically performed by the Matlab program using the following steps: (i) the solenoid valve opens for 0.1 s and then closes. (ii) The camera records a sequence of 30 images at 166 fps. (iii) The syringe pump (see Fig. 1c) withdraws air at 10 mL/min for 0.15 s, thus replacing all the particles in the FoV by new particles not yet sampled. (iv) Two additional image sequences are recorded by repeating steps (ii) and (iii)

twice more, thus increasing the amount of sampled particles by a factor of 3. Note that the data were observed to be very similar between the three image sequences; yet, additional image sequences were not recorded in order to avoid bias of the results due to selective particle loss by gravity. The time interval in which the solenoid valve was open was empirically optimized to increase the amount of detected particles. We found that 0.1 s was the optimal time interval in our system and that longer or shorter intervals resulted in reduced numbers of detected particles. Nevertheless, the optimal time interval may slightly vary for different flow rates and inhalers. The flow chamber was manually cleaned using DI water and an interdental brush following approximately 10 measurements. Future designs may include disposable chambers which can be quickly replaced when necessary.

2.2.6 Image processing and analysis—All image and data analysis procedures were conducted using Matlab (version R2015b), and an in-house code. To improve the quality of the raw images prior to particle detection and tracking, background subtraction was first applied to the raw images by subtracting the mean intensity of the entire image sequence (i.e. 30 frames) from each individual frame. In addition, the resulting images were smoothed by a 5×5 pixel Gaussian filter.

The threshold intensity for identification of particles was set prior to initiation of the experiments. Particle locations were then determined as the intensity weighted centroid of all pixels in the detected area having an intensity above 70% of the maximal intensity in this region of interest. By setting a different threshold for each detected particle this double-threshold procedure ensures accurate measurement of particle locations despite a broad range of particle sizes and intensities. Particle tracks were then calculated based on the assumption that the nearest detections in two consecutive images arise from the same particle.

2.2.7 Calculation of aerodynamic diameter distributions—The aerodynamic particle diameter, d_p , for each individual particle was calculated following Eqs. (1) and (2),

$$d_p^2 = \frac{18\mu u_t}{\rho_p g C_c}, \quad (1)$$

$$C_c = 1 + 2.52 \frac{\lambda}{d_p}, \quad (2)$$

where μ is the dynamic viscosity of air, u_t is a particle's (vertical) terminal velocity, ρ_p is the particle density, g is the gravitational acceleration, C_c is the Cunningham slip correction factor approximated by the expression given in Eq. (2) for particles larger than $0.1 \mu\text{m}$ (Finlay, 2001), and $\lambda \sim 0.067 \times 10^{-6} \text{ m}$ is the mean free path for air.

Mass weighted histograms were subsequently calculated by assuming particles of spherical shape with a uniform density. Note that in order to compare our results to CI measurements particle size bins were chosen to match corresponding cascade impactor measurements

available in the literature (see Results and discussion section). Nevertheless, the optimal choice of size bins for our method remains to be determined in future work.

2.2.8 ToF analysis—ToF analysis was conducted using an aerodynamic particle sizer (APS 3321, TSI) equipped with a 3302A TSI Diluter, a 3306 TSI Impactor Inlet and a standard USP inlet throat provided with the impactor setup. The maximal flow through the impactor from the available vacuum pump (high power vacuum pump: Erweka HVP 1000) was 55 L/min, and therefore all samples were measured at 55 L/min. The flow through the setup was measured using a TSI 4021 flowmeter. Since not all parameters are known for the medicines measured, a particle density of 1.52 g/cm³ was assumed for applying the stokes correction. Mass weighted histograms were calculated from the number distributions by assuming particles of spherical shape with a uniform density. Adhesive putty was used to achieve an airtight connection to the DPI. To compare the ToF results to the CI and the prototype (Fig. 4), the size bins of the APS were united to size bins corresponding to cutoff aerodynamic diameters in the CI measurements. In regions where a ToF size bin overlapped two different CI size bins its mass content was divided between the two size bins by a linear interpolation scheme, i.e., the ratio of masses was equal to the ratio of aerodynamic size intervals.

3 Results and discussion

We begin by presenting concept testing experiments using commercially-available DPIs and corresponding data available in the literature. While the first step in evaluating an aerosol measurement technique is usually based on the measurement of monodispersed particles, we have chosen at present to delay such measurements to a later stage of product development. The rationale for such approach lies in that the underlying novelty of our prototype is not founded in the principle of measurement, which has been similarly applied before (Stahlhofen et al., 1975) and relies on the very definition of the aerodynamic diameter. Instead, the uniqueness of the current design is the ability to probe particle distributions from medical inhalers, where specifically very dense aerosols of polydispersed particles are generated, and the aerosol should be actively drawn from the inhaler by means of a relatively high flow rate. We therefore have focused in the current study on measuring size distributions from commercial DPIs to assess the feasibility of obtaining meaningful particle measurements for real drug formulations, and delay experiments with monodispersed particles to future work (see below). Fig. 4 shows mass weighted aerodynamic size distributions for four different DPIs measured using our present prototype. For comparison, measurements that we performed on the exact same inhalers using ToF analysis are also shown. In addition, we include data from the literature obtained using CIs. For details and references see caption of Fig. 4; mass median aerodynamic diameters (MMAD) and geometric standard deviation (GSD) for these inhalers are summarized in Table 2 where the corresponding measurements using CIs and ToF are also shown. For these calculations, the full ToF data including all size bins were used and not the newly divided size bins that were used in Fig. 4. Note that the comparison of measurements from our prototype to ToF analysis is more meaningful than a comparison to CI data since the CI data exclude excipient particles that do not contain the drug. In addition, we emphasize that while some

of the results in Fig. 4 may not seem to be log-normally distributed they are in-fact close to log normal as observed in ToF measurements.

While relatively accurate results are obtained with smaller size particles (e.g. for Eklira, see Fig. 4b), we observe on the other hand an overestimation of MMADs for larger particles (e.g. for Seretide, Foradil, and Spiriva). For these inhalers, MMAD values measured using the prototype were statistically found to be different from the corresponding measurements using ToF analysis following a two-tailed t -test with unequal variances (i.e. $p < 0.05$, $p < 10^{-7}$, $p < 10^{-8}$ for Seretide, Foradil and Spiriva, respectively). A similar analysis for Eklira yielded $p = 0.05$ suggesting relatively close results. In addition, MMAD values were significantly different between prototype and CI measurements for all the tested inhalers using the same analysis described above (i.e. $p < 0.0001$, $p < 0.05$, $p < 0.0001$, $p < 0.01$ for Seretide, Eklira, Foradil and Spiriva, respectively).

The bias observed in the MMAD estimation using our prototype can be attributed in part to the fact that smaller particles are detected only when their distance from the focal plane is sufficiently small to allow a peak intensity level that is higher than the set threshold value. As a result, fewer of the smaller particles are counted compared to larger ones that can be detected at larger distances from the focal plane. This bias can in principle be corrected using a proper calibration scheme, for example using monodispersed aerosols in conjunction with aerosol density measurements. In such measurements, which are out of the scope of the current study, a dense aerosol of monodispersed articles can be first measured using a condensation particle counter to obtain the particle density, and then measured by the prototype to obtain a particle count and a size distribution. The size distribution can be used to validate the accuracy of the measurement principle, and the number of particles can be used to correlate the number of measured particles to a particle density. By repeating the experiment with several particle sizes, a calibration curve can be constructed to correct for size dependent detection rates.

Other sources identified for discrepancies between our results and CI results stem from the presence of excipient particles (Lactose), the assumptions of spherical particles and homogeneous density, and possible differences in particle distributions between the inhalers used in this study and the ones used in the cited articles. In addition, differences in our results compared to both CIs and ToF analysis may stem from the difference in the induction port geometry (see Prototype design section). Furthermore, we note that inaccuracies in the present prototype are larger for models of inhalers where fewer particles are counted at each experiment. Note that the variability in the number of detected particles is a result of a combination between the variability of aerosol densities between different inhalers and the fact that products with larger MMADs contain fewer particles for a similar drug mass. For example, the average number of counted particles for Seretide Diskus (Fig. 4a) was 405 compared to 1170 particles for Eklira Genuair (Fig. 4b). A better design would likely require a means to measure larger numbers of particles belonging to the larger size bins by adding for example an additional imaging system with a larger FoV. Despite limitations of the current prototype design, it is important to view our results in the context of the inherent discrepancies that currently exist across the different measurement methods (see for example differences between the CI and ToF results in Fig. 4c). Overall, these benchmark

experiments demonstrate the feasibility of obtaining aerodynamic size distributions from medical inhalers by direct measurement of particle settling velocities, thus providing fast results (within ~1 min) in a simple device. While in this study only DPIs were used, the same methods can in principle also be adapted for nebulizers and pressurized metered dose inhalers (pMDIs) by using, for example, compensatory calculations for droplet evaporation or minimizing the evaporation (e.g. by humidifying or cooling the air).

4 Conclusion

In a proof-of-concept study, we have obtained aerodynamic particle size distributions from various widely-available commercial DPIs using a simple flow device and computer-vision based analysis of settling velocities. Furthermore, we have shown that our results correlate with benchmark measurements obtained using standard characterization methods. Our prototype stands in line with current fast inhaler characterization methods on the market. Specifically, it features high throughput and precise measurement of particle aerodynamic diameters similarly to ToF analysis (see Table 1), while circumventing some of the potential biases of the ToF technique (see Rationale and overview of the prototype section). Indeed, the ability of our method to directly image drug particle samples as they settle in air and calculate their settling velocities increases its credibility compared to other indirect methods. With some improvements, this measurement system can serve as a cost-effective alternative to existing methods, and could be particularly appealing for lean startup companies and research laboratories. In particular, due to the simplicity of the proposed system we suggest that research laboratories could construct their own particle sizing system from off-the-shelf equipment and materials. Foreseeable future work will include testing the measurement accuracy and improving the calibration of the system by performing experiments with monodispersed particles, and improving the repeatability for larger particles by adding a second imaging system with a larger field of view, and thus increasing the number of detected particles. Furthermore, the capabilities of our measurement apparatus will be expanded for obtaining measurements from other inhalation devices, including pressurized metered dose inhalers (pMDIs).

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Fig. 1. Prototype of the measurement device. Schematic illustration of (a) the particle sizer setup, (b) a front view of the flow chamber and (c) details of the flow control unit.

Fig. 2. Exploded view of the CAD design of the flow chamber. The chamber is composed of 1 mm thick glass plates and has inner dimensions of 1.5 mm $\times$ 12 mm.

Fig. 3.

Theoretical 1D light diffraction pattern assuming Fresnel–Kirchhoff diffraction. Normalized light intensity as a function of distance from the focal plane (z) is presented for the bottom, middle and top of the camera field of view. The y - z coordinate system is illustrated in Fig. 1b.

Fig. 4.

Comparison of mass fraction results for four different drug-DPI combinations obtained experimentally using the prototype system, ToF analysis using an aerodynamic particle sizer (APS), and data from the literature obtained using CIs. The drug-DPI combinations used and sources for CI data are: Seretide® Diskus® 50/100 mcg Lot GY8V exp. 12 2016 (Daley-Yates et al., 2013); the CI data are based on Salmeterol deposition; Eklira® Genuair® 322 mcg Lot 2J Exp. 01 2017 (Block and Fyrnys, 2010); Foradil® Aerolizer® 12 mcg Lot U0060 exp. 08 2014 (Alaboud, 2013), Spiriva® Handihaler® 18 mcg Batch No. 504317 Exp. 03 2017 (Shur et al., 2012). Error bars represent standard deviation (SD) with $n = 9-12$ for prototype measurements and $n = 4$ for APS measurements. Number of measurements for CI data was unavailable.

Table 1

Comparison between various aerosol sizing techniques.

	High throughput	Aerodynamic size measurement	Operates without dilution or preseparation	Direct measurement of mass weighted size distributions	Chemical specificity	Electrostatic charge measurement
CI	–	+	Sometimes	+	+	–
ToF	+	+	–	–	–	–
E-SPART	+	+	–	–	–	+
SPLS	+	–	–	–	–	–
LD	+	–	+	+	–	–
ELPI	+	+	Sometimes	–	–	+
SPAMS	+	+	–	–	+	–
Present device	+	+	+	–	–	–

Table 2

Summary of particle measurements (i.e. average MMAD and GSD) for different DPIs using our prototype as compared to values from the available literature. Standard deviations are reported based on data availability.

Inhaler	Flow rate (L/min)	MMAD			GSD		
		CI	ToF	Prototype	CI	ToF	Prototype
Seretide	60	4.1 ± 0.1	4.6 ± 0.7	6.0 ± 0.7	2.0 ± 0.03	1.9 ± 0.1	1.7 ± 0.1
Diskus							
Eklira	65	2.3	2.3 ± 0.1	2.5 ± 0.2	1.8	1.6 ± 0.1	1.5 ± 0.1
Genuair							
Foradil	60	5 ± 0.1	3.4 ± 0.1	6.5 ± 0.8	2.1 ± 0.1	1.7 ± 0.03	1.6 ± 0.1
Aerolizer							
Spiriva	55	4	2.9 ± 0.1	4.7 ± 0.7	1.8	1.6 ± 0.1	1.8 ± 0.1
Handihaler							