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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.

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, 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

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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	+	+	+	−	−	−

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/m^3 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 (~100 μm) 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