Isokinetic In-line Sampling Enables Rapid Characterization of Atomizers and Cyclones for Spray Drying Process Development

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INTRODUCTION

In the competitive inhalation space, researchers developing the next generation of dry powder inhaler (DPI) and pressurized metered dose inhaler (pMDI) products have focused attention on tailoring the properties of the drug or carrier particles to maximize the efficiency and repeatability of drug delivery [1-3]. Spray drying is an attractive process for producing such engineered particles since critical physical properties such as size, particle density, dispersibility, or flowability can be manipulated by modifying the formulation and process parameters [4]. Achieving such control requires knowledge about the process equipment itself: the size distribution of the collected dried particles depends strongly on the atomized droplet diameter distribution [5], and may be influenced by the means of collection as well [6]. Therefore, attaining reliable performance specifications for atomization and collection equipment is valuable in enabling the development of quantitative relationships between the formulation and process parameters, and the critical quality attributes of the powder. To this end, an isokinetic aerosol sampling system was developed. The system was used to characterize the performance of an atomizer and cyclone supplied with a popular pharmaceutical lab scale spray dryer (B-290, Büchi, Flawil, Switzerland).

METHODS

Real-time measurements of the aerodynamic particle size distribution of aerosols at various sampling locations within the drying process were attained using a variable flow rate isokinetic sampling system. The system is depicted schematically in Figure 1; it incorporates a time-of-flight aerodynamic particle sizer (Model 3321, TSI, Shoreview, MN, USA), and was integrated into a custom laboratory-scale spray dryer. Atomized droplet mass median diameter ($d_{0,50}$) and geometric standard deviation (GSD_0) were measured indirectly by atomizing and drying disaccharide solutions of known concentration (c_s). Dried aerosols were sampled and measured upstream of the cyclone separator. Assuming spherical particles of known particle density (ρ_p), droplet size distribution parameters were computed based on the measured mass median diameter ($d_{a,50}$) and breadth (GSD_a) of the aerodynamic diameter distribution of the dried aerosol (ρ^*= 1000 kg/m^3):

$$d_{0,50} = \sqrt[3]{\frac{\rho^*}{c_s}}\sqrt[6]{\frac{\rho^*}{\rho_p}}\, d_{a,50} \text{ with } GSD_0 = GSD_a \qquad \textit{Equation 1}$$

Cyclone separation efficiency curves were determined by measuring the aerodynamic diameter distributions of the feed (inlet) and the overhead (outlet) fractions: for the i-th diameter bin (x_i) the fractional efficiency ($\eta(x_i)$) was computed based on the discrete count distributions of the feed and the overhead fractions ($f_F(x_i)$ and ,$f_O(x_i)$ respectively.

$$\eta(x_i) = 1 - \frac{f_O(x_i)}{f_F(x_i)} \qquad \textit{Equation 2}$$

Atomization and collection equipment supplied with the Büchi B-290 was characterized with the sampling system. Atomized droplet diameter distributions were measured for a twin fluid atomizer with a 0.7 mm liquid nozzle diameter and a 1.5 mm diameter gas cap. Cyclone separation efficiency was determined at three gas flow rates for Büchi's "high efficiency" cyclone design.

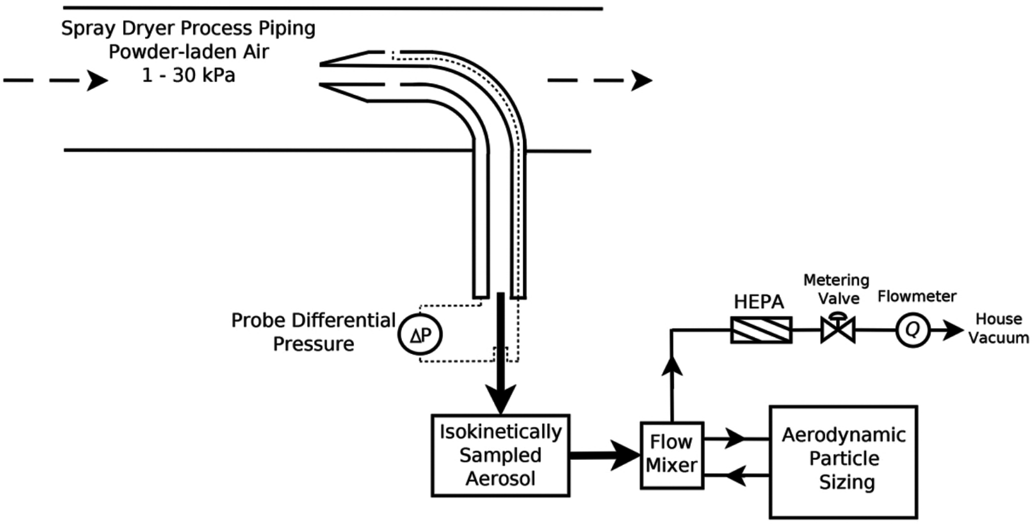

Figure 1. **Schematic depiction of the isokinetic sampling system, which enabled real-time measurement of the aerodynamic particle size distribution of aerosol in the drying process at varying locations within the drying process.**

RESULTS AND DISCUSSION

The response of the atomized droplet mass median diameter as measured using Equation 1 to changes in the atomizing air-liquid mass ratio is presented in Figure 2 for water sprays at 2, 5, or 8 mL/min and for ethanol at 5 mL/min. Measured geometric standard deviation varied from 1.4 to 1.7 with a mean of 1.6 across all sprays, and was not obviously correlated with any parameter. A substantial degree of control on the atomized droplet diameter can be attained by manipulating the air-liquid ratio: for a given flow rate, this is achieved by modifying the atomizing air pressure. With this data, the mass median diameter for powders produced from solutions can be estimated provided an estimate is available for ρ_p:

$$d_{\mathrm{p},50} = \sqrt[3]{\frac{c_\mathrm{s}}{\rho_\mathrm{p}}}\, d_{0,50} \qquad \textit{Equation 3}$$

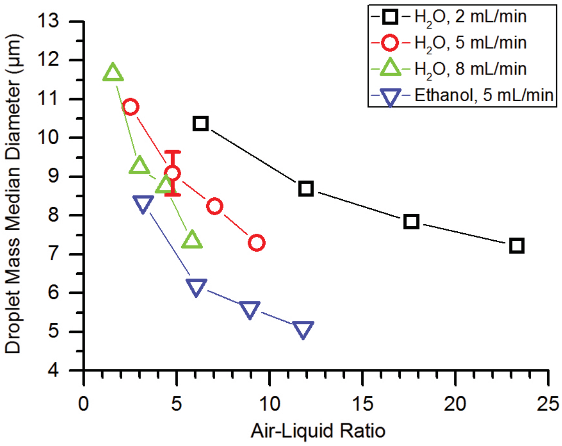

Figure 2. **Mass median droplet diameter vs. atomization air-liquid ratio for the tested Büchi twin fluid atomizer. An intermediate point was replicated three times to assess measurement variability. The error bar represents one standard deviation.**

Cyclone separation efficiency curves for the high-efficiency cyclone operating at 100, 200, and 300 standard liters per minute (SLPM) gas flow rate are presented in Figure 3. Due to measurement range limitations of the aerodynamic particle size measurement system, extrapolation was required to estimate the 50% cut size of the cyclone operating at the highest tested flow rate. This was done using nonlinear curve fitting, with functional form

$$\eta(x) = 1 - \exp\left[\ln\left(\frac{1}{2}\right)\left(\frac{x}{x_{50}}\right)^{m}\right] \qquad \textit{Equation 4}$$

Noting that the typical operating flow rate for a 100% aspirator setting is roughly 300 SLPM, this cyclone is expected to offer very high efficiency collection of typical powders for inhalation.

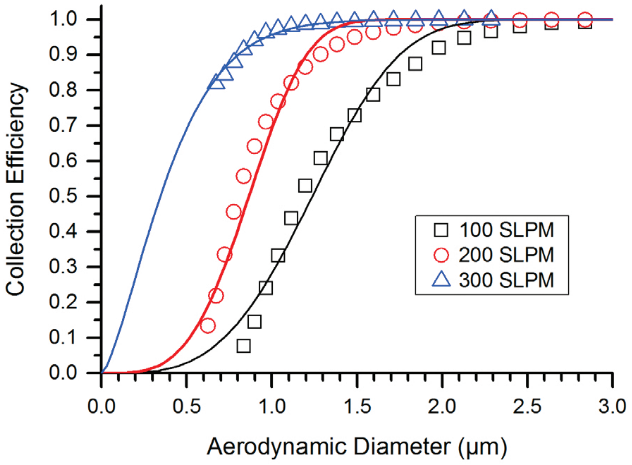

Figure 3. **Separation efficiency curves for Büchi's high-efficiency cyclone separator at air flow rates of 100, 200, and 300 SLPM. Symbols: measured data using Equation 2. Closed lines: curve fits using Equation 4. 50% cut size from curve fits: 1.24 µm at 100 SLPM, 0.84 µm at 200 SLPM, and 0.35 µm at 300 SLPM.**

CONCLUSIONS

The new isokinetic sampling system allows real-time measurement of the aerodynamic particle size distribution in spray drying processes. The utility of the technique is demonstrated by rapidly characterizing the atomizer and cyclone of a commercially available lab scale spray dryer. Indirect measurements of atomized droplet diameter distributions enable estimation of the dry particle size distribution for solution-based drying processes. Measured cyclone collection efficiency curves indicate that the tested cyclone is capable of collecting even sub-micron particles with high efficiency. These equipment performance data are required for process models which quantify the relationships between the formulation and drying process parameters and the physical properties of the dried powders. Such mechanistic models can reveal critical process parameters and streamline process development, resulting in substantial savings in both time and capital.

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Notes