An *In-Silico* Investigation of Formulation and Droplet Size Effects on the Aerodynamic Particle Size Distributions of Suspension Pressurized Metered Dose Inhalers

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Introduction: To provide effective treatment, pressurized metered dose inhalers (pMDIs) must produce drug particles with a small aerodynamic particle size distribution (APSD). The equilibrium APSD produced by solution pMDIs can be controlled by manipulating the concentration of nonvolatile solutes [1]. With suspension formulations, the matter is somewhat more complex: atomized propellant droplets may contain zero, one, or multiple particles (multiplets) of the suspended phase. Multiplets result in coarsening of the APSD, and their frequency depends on the concentration and size distribution of the suspended particles in the metering chamber and the size distribution of the atomized droplets. This effect is of particular importance for high dose suspension pMDIs, which may require relatively high concentrations of suspended drug in the propellant. Since the problem of sorting polydisperse suspended particles into polydisperse droplets has not been solved analytically, researchers have relied on stochastic modeling techniques to explore the effects of drug size distribution and concentration on the APSD of the aerosol following evaporation of the volatile phase [2-8]. In this work, a stochastic model was utilized to further explore these effects, and an analytical equation was derived for general use.

Methods: A stochastic model was developed to simulate sorting of suspended particles into atomized droplets and assess the particle size distribution present after

evaporation of the volatile phase; the basic functionality is depicted in Figure 1. The model was implemented in C++. The spray of droplets and the suspended phase were assumed to be made up of spheres with known lognormal size distributions. After generating a sorted array of $N_0 = 10^6 - 10^7$ droplets, the number of suspended particles to simulate, N_{sp}, was calculated (please see Table 1 for variable definitions) using the Hatch-Choate conversion equations [9]:

$$\frac{N_{\mathrm{sp}}}{N_0} = \frac{c_{\mathrm{sp}}}{\rho}\left[\frac{d_{0,50}\exp(-\frac{3}{2}\ln^2 GSD_0)}{d_{\mathrm{sp},50}\exp(-\frac{3}{2}\ln^2 GSD_{\mathrm{sp}})}\right]^3 \quad (1)$$

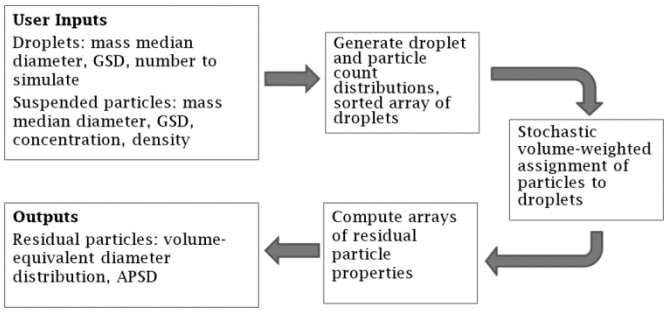

Figure 1: Flow chart describing the function of the stochastic model.

Then particles of suspended phase were assigned to droplets using a volume-weighted random assignment scheme, with the total volume of suspended phase contained in each droplet tracked throughout. In rare cases where the volume of suspended particle(s) assigned to a droplet, V_{sp_i}, exceeded the droplet volume, V_{0_i}, the droplet volume was increased: $V_{0_{i,\mathrm{new}}} = V_{0_i} + V_{\mathrm{sp}_i}$.

In the case of multiplets, packing effects were neglected by coalescing the constituent particles into a single larger sphere. Droplets were then "evaporated" and the residual particle volume equivalent and aerodynamic diameters ($d_{\mathrm{v}_i}, d_{\mathrm{a}_i}$, respectively) were

computed: $d_{\mathrm{v}_i} = \frac{6}{\pi} \sqrt[3]{V_{\mathrm{sp}_i}}$, $d_{\mathrm{a}_i} = \sqrt{\frac{\rho}{\rho^*}}\, d_{\mathrm{v}_i}$. Here shape effects have been neglected for simplicity, which for irregular particles will tend to result in some systematic overestimation of the aerodynamic diameter. Finally, mass-weighted frequency distributions were computed and output; data analysis was conducted using Excel 2010 (Microsoft, Redmond, WA, USA) and Origin 2018 (OriginLab, Northampton, MA, USA). Model results were compared to experimentally determined APSDs of suspension pMDIs containing varying concentrations of micronized fluticasone propionate (pMDI droplet $d_{0,50}$ 9.6 ± 0.7 µm, GSD_0 1.5, suspended material c_{sp} 0.9 – 11.8 mg/mL, $d_{\mathrm{sp},50}$ 1.2 ± 0.1 µm, GSD_{sp} 1.7). APSDs of these pMDIs were determined by actuating inhalers into a 30 L evaporation chamber and prolonged sampling using a time of flight aerodynamic particle sizer (Model 3321, TSI Inc., Shoreview, MN, USA). A total of 90 sets of conditions were simulated using the model; evaluated parameter ranges are summarized in Table 1.

Table 1: Parameter ranges evaluated herein; suspended phased density $\boldsymbol{\rho}$ = 1365 kg/m^3 in all cases

Input Parameter	**Range Evaluated**
Droplet mass median diameter $d_{0,50}$	9 - 36 µm
Droplet geometric standard deviation GSD_0	1.5 – 2.1
Suspended phase concentration c_{sp}	0.06 - 256 mg/mL
Suspended phase mass median diameter $d_{\mathrm{sp},50}$	1.0 – 5.0 µm
Suspended phase geometric standard deviation GSD_{sp}	1.5 – 2.1

Results and Discussion: As illustrated in the left panel of Figure 2, model results were in reasonable agreement with experimentally determined APSDs, indicating that the set of model assumptions is suitable to describe the problem. As previously

reported by researchers utilizing similar models [6, 7] and as illustrated in the right panel of Figure 2, the model predicts that for constant GSD_0 and GSD_{sp} the ratio of the MMAD of the aerosol emitted by the pMDI to the MMAD of the micronized suspended particles, Γ, increases for increasing suspension concentration. The rate of increase is dependent on the ratio of the median droplet diameter to the median suspended particle diameter, $d_{0,50}/d_{\mathrm{sp},50}$. As shown in the left panel of Figure 3, for constant GSD_0 and GSD_{sp} the growth factor Γ collapses to a single curve when plotted against the suspended particle to droplet number ratio, $\frac{N_{\mathrm{sp}}}{N_0}$. Further, the rate of increase of Γ for increasing $\frac{N_{\mathrm{sp}}}{N_0}$ depends quite strongly on the ratio of GSD_0 to GSD_{sp}. To enable utilization of these results for researchers without access to the stochastic model itself, Γ values from a subset of simulation data covering a wide range of all input parameters was fit as a training set using nonlinear least squares regression:

$$\Gamma = \left[0.939 \ln\left(\frac{N_{\mathrm{sp}}}{N_0} + 3.42\right)\right]^{1.03 GSD_0/GSD_{\mathrm{sp}}}, \quad R^2_{\mathrm{adj}} = 0.96 \tag{2}$$

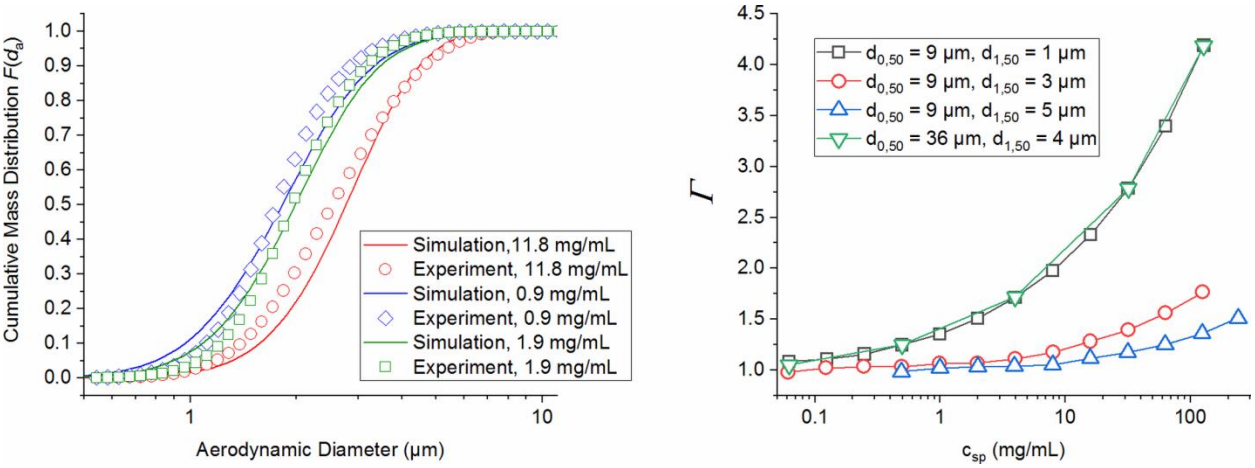

Figure 2: Left panel: comparison of simulated and selected measured cumulative APSDs for suspension metered dose inhalers containing different concentrations of fluticasone propionate. Right panel: effect of droplet and suspended phase median diameter and suspension concentration on the growth factor $\boldsymbol{\Gamma}$ for $\boldsymbol{GSD_0 = 2.1}$ and $\boldsymbol{GSD_{\mathrm{sp}} = 1.8}$.

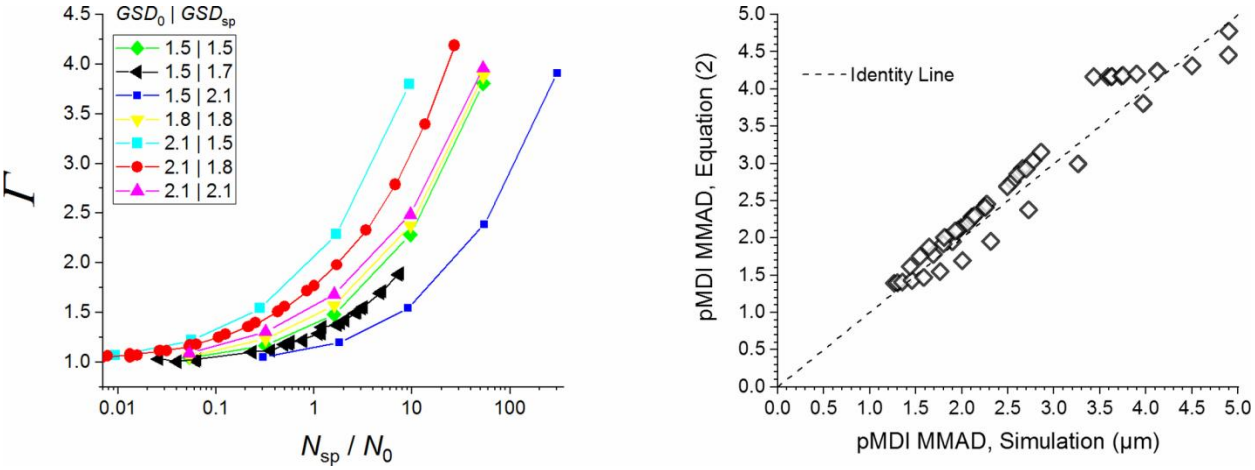

Figure 3: Left panel: dependence of growth factor $\boldsymbol{\Gamma}$ on the suspended particle to droplet ratio $\frac{\boldsymbol{N_{sp}}}{\boldsymbol{N_0}}$ for varying $\boldsymbol{GSD_0}$ and $\boldsymbol{GSD_{sp}}$. Right panel: pMDI MMAD values as predicted using Equation (2) vs. stochastic model predictions.

Equation (2) was then used to estimate the MMAD for the remaining simulated conditions; as shown in the right panel of Figure 3, Equation (2) provides estimates in reasonable agreement with the actual simulation results.

Conclusions: The stochastic modeling technique used here accurately predicts the APSD of suspension pMDIs and enables *in-silico* explorations of the input parameter space. While the effects of suspension concentration, atomized droplet diameter, and suspended particle size on the APSD of solution pMDIs are well-documented, this work indicates that the breadth of the droplet size distribution and the breadth of the suspended phase size distribution may also have a strong effect on the APSD for high suspension concentrations or for fine suspended material. By utilizing the curve fit of Equation (2), the results can be applied by practitioners in industry without the need to develop complicated models. These findings suggest that repeatable drug delivery from a suspension pMDI—whether through the life of a single inhaler or the life cycle of a product—requires a robust device capable of producing consistent spray characteristics coupled with a well-controlled, stable suspension formulation.

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