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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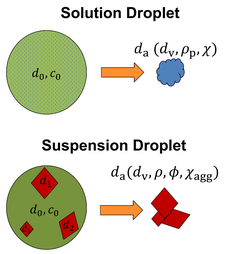
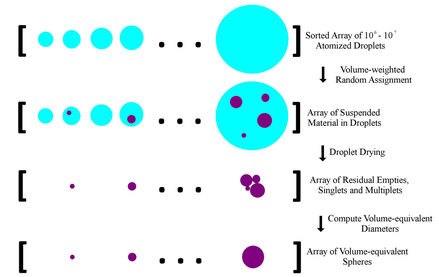
Introduction

- Effective treatment from pMDIs requires drug aerosol with small aerodynamic particle size distribution (APSD)
- Solution pMDIs: one particle / droplet; atomized droplet size ↔ drug APSD; drug APSD tunable with nonvolatile additives [1]
- Suspension pMDIs: generally < 1 drug particle / droplet; production of multiplets → $MMAD_{\mathrm{pMDI}} \neq MMAD_{\mathrm{sp}}$
- Stochastic models are capable of quantifying multiplet-driven coarsening [2-8]
  - Coarsening worst for high dose suspensions or very fine suspended phase
- A stochastic model was developed to further explore these effects, and an analytical equation was derived for general use.

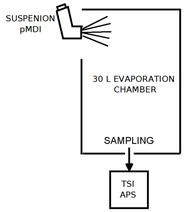


Materials and Methods

- A stochastic model was developed in C++ to simulate random sorting of suspended particles into atomized droplets
- Droplets and particles were assumed to be spherical with lognormally distributed diameters
- Based on user inputs, the number of suspended particles in the simulation was calculated using the Hatch-Choate conversion equations **[9]**
- Particles were assigned to droplets using a volume-weighted random assignment scheme
- In rare cases where suspended phase volume exceeded droplet volume, droplet volumes were increased : $V_{0_{i,\mathrm{new}}} = V_{0_i} + V_{\mathrm{sp}_i}$
- For multiplets, packing effects were neglected by coalescing particles into a single larger sphere of equal volume
- Droplets were 'evaporated' and the volume equivalent and aerodynamic diameters were computed: $d_{\mathrm{v}_i} = \frac{6}{\pi}\sqrt[3]{V_{\mathrm{sp}_i}}$, $d_{\mathrm{a}_i} = \sqrt{\frac{\rho}{\rho^*}}\, d_{\mathrm{v}_i}$

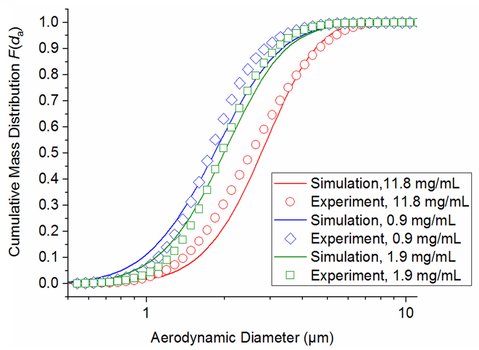


Input Parameter	Range Evaluated
Droplet mass median diameter $d_{0,50}$	9 - 36 µm
Droplet geometric standard deviation GSD_0	1.5 – 2.1
Suspended phase concentration c_{sp}	0.06 - 256 mg/mL
Suspended phase density ρ	1365 kg/m³
Suspended phase mass median diameter $d_{\mathrm{sp},50}$	1.0 – 5.0 µm
Suspended phase geometric standard deviation GSD_{sp}	1.5 – 2.1

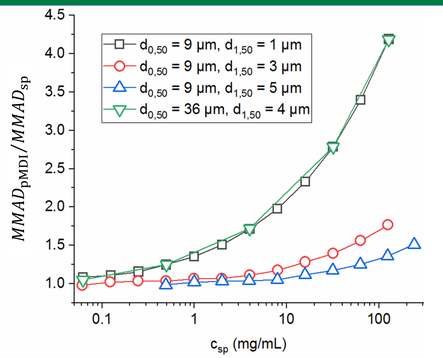


- Model results were compared to experimentally determined APSDs of suspension pMDIs with varying drug concentration and known droplet and suspended phase size distributions
- Sprays were allowed to evaporate fully at ambient lab conditions in a large volume chamber prior to sampling with a time-of-flight aerodynamic particle sizer (Model 3321, TSI, Shoreview, MN)

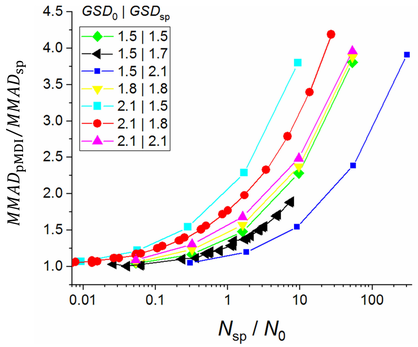
Results



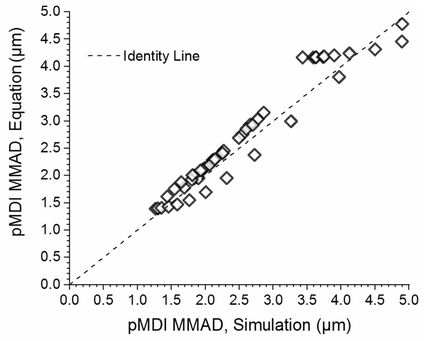
Model results are in good agreement with time-of-flight APSD measurements of suspension pMDIs with varying suspension concentration



Growth factor $\Gamma = MMAD_{\mathrm{pMDI}}/MMAD_{\mathrm{sp}}$ depends on suspension concentration and drug:droplet size ratio. Results for $GSD_0 = 2.1$ and $GSD_{\mathrm{sp}} = 1.8$.



For constant GSD_0 and GSD_{sp}, growth factor collapses onto a single curve when plotted against the drug particle : droplet number ratio. The growth rate is highly dependent on the breadths of the droplet and drug particle size distributions.



A nonlinear least squares fit (adj. R^2 = 0.96) to a training data set provides reasonably accurate predictions of subsequent simulation runs; the fit enables model results to be utilized by those without access to the full modeling capabilities.

➢ Predictive Equations for Suspension pMDI MMAD

$$\frac{N_{\mathrm{sp}}}{N_0} = \frac{c_{\mathrm{sp}}}{\rho}\left[\frac{d_{0,50}\exp(-\frac{3}{2}\ln^2 GSD_0)}{d_{\mathrm{sp},50}\exp(-\frac{3}{2}\ln^2 GSD_{\mathrm{sp}})}\right]^3 \qquad \frac{MMAD_{\mathrm{pMDI}}}{MMAD_{\mathrm{sp}}} = \left[0.939\ln\left(\frac{N_{\mathrm{sp}}}{N_0}+3.42\right)\right]^{1.03GSD_0/GSD_{\mathrm{sp}}}$$

Conclusions

- The model accurately predicts the APSD of real suspension pMDIs, enabling rapid exploration of the formulation parameter space *in silico*.
- Curve fitting enables utilization of results by those without access to the full modeling capabilities.
- The extent of particle size coarsening due to the presence of multiplets depends not only on droplet size, drug particle size, and drug concentration, but also on the breadths of the distributions of drug particles and droplets.
- This finding is especially relevant for high dose suspension pMDIs or those containing ultrafine particles.
- The results indicate that repeatable drug delivery with suspension pMDIs requires tight controls on microcrystalline drug particle size distribution and factors influencing the atomized droplet diameter distribution.

References

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