Characterization of Dry Powder Aerosols of Albuterol Sulfate/Lactose Monohydrate and Cromolyn Sodium/Lactose Monohydrate Delivered by Standardized Entrainment Tubes

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MOTIVATION

Standardized entrainment tubes (SETs) with defined flow parameters provide a great opportunity to examine the dispersion of various batches of Respitose products. Together with other powder techniques, they are aimed to shed light on the fundamental characteristics of pharmaceutical dry powder formulation, and to achieve performance prediction.

OBJECTIVE

To evaluate the effects of morphology, lactose grade, and surface energetics on *in vitro* aerosolization and particle deposition of drug/lactose blends using SETs with varying shear stress and power.

MATERIAL

Pulmonary Drugs

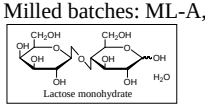
Micronised **Albuterol Sulfate** ($C_{13}H_{23}NO_7S$)

Micronised **Cromolyn Disodium** ($C_{23}H_{14}Na_2O_{11}$)

Respitose Carriers

Lactose monohydrate ($C_{12}H_{22}O_{11}$)

- MW 342.30 g/mol;
- Analysis led to selection of four batches;
- Sieved batches: SV-A, SV-B;
- Milled batches: ML-A, ML-B.



METHODS

Particle sizing was performed using Malvern laser diffraction for volume particle size distribution and inertial sampling aerosol particle sizing techniques for aerodynamic particle size.

Drug/lactose interactive physical mixtures were prepared at drug concentrations of 0.5%(w/w) and 2% (w/w). Solid–state characterization of phase behavior and molecular interactions was performed using differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD).

Particle morphology was examined using scanning electron microscopy (SEM). Atomic force microscopy (AFM) was utilized for topographical imaging and surface energetics characterization of these drug powder particulate systems.

METHODS

Aerosol dispersion, distribution, and performance were assessed and characterized by twin-stage liquid impinger (TSLI) to measure the proportion of the aerosol particles delivered in a sized range less than 6.4 mm and Anderson 8-stage non-viable cascade impactor (ACI) as an *in vitro* lung model of aerosol particle deposition. Aerosolization was performed using a series of SETs with well-defined shear stress (τ_s), Renolds number (Re), pressure drop (ΔP) and power. (Q=60 L/min) Dispersion data were evaluated with Design-Expert ver. 5.0.9, 2-level full factorial analysis.

Inhaler device / SET	Specific Resistance (R_D) ($cmH_2O^{0.5}$/(L/min))	Regression Coefficient (r^2)
Tube A	0.140	0.992
Tube B	0.065	0.993
Tube C	0.046	0.998
Tube D	0.021	0.994

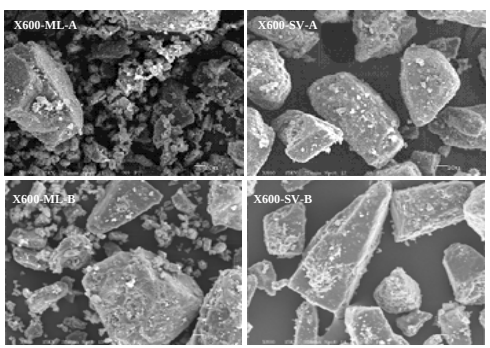
RESULTS & DISCUSSION

Jet-milled drug particles were in the respirable sized range (< 5 mm) with a narrow normal size distribution (Span < 0.5).

	Span	D_{10}	D_{50}	D_{90}
Alb#	**0.26±0.09**	**3.20±0.06**	**3.59±0.13**	**4.13±0.40**
Crom#	**0.32±0.01**	**3.24±0.01**	**3.68±0.02**	**4.40±0.04**
SV-A*	1.1-1.2	29.0	61.4	104.7
SV-B*	1.1-1.2	31.5	59.7	97.3
ML-A*	~3.1	4.20	54.6	174.9
ML-B*	~3.1	4.13	52.0	167.5

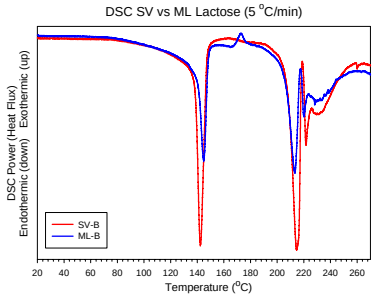
 # Mean and standard deviation, n = 2.

** The particle size distributions of the four selected lactoses as supplied by the manufacturer.*

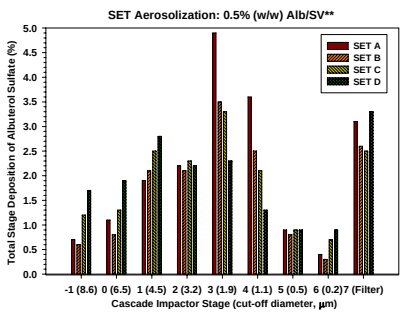


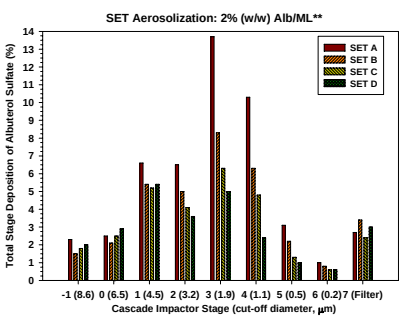
SV batches have more uniform particle morphology, distribution, fewer particle aggregation and narrower particle size distribution than ML batches.

RESULTS & DISCUSSION



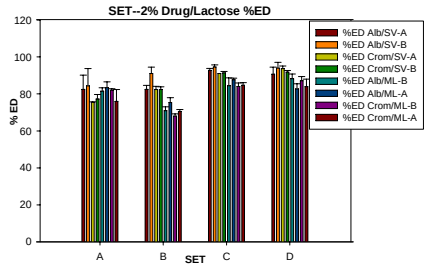
DSC measurement revealed distinct difference between SV and ML batches, and scanning rate dependent transitions for both ML and SV. Quantitative analysis of transition temperature (T_m) and enthalpy (ΔH) revealed that remarkable changes following different drug blending, with endothermic peak broadening and increased molecular disorder, and the exothermic peak enhancement.

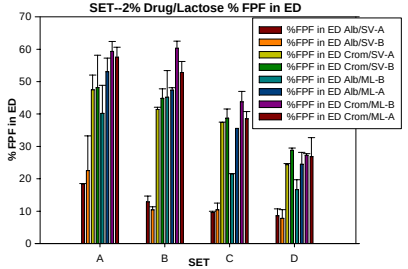




*** Device, throat, and pre-separator drug depositions are not shown in the graphs.*

RESULTS & DISCUSSION





For all aerosol systems studied, the lowest shear stress SET (τ_s = 0.624 N/m^2) gave a higher emitted dose (ED = 83~94%) but lower fine particle fraction ($FPF_{6.4}$ = 8~29%).

Contrastingly, the highest shear stress SET (τ_s = 13.143 N/m^2) gave a relatively lower emitted dose (ED = 76~84%) but a significantly higher fine particle fraction ($FPF_{6.4}$ = 18~59%) than the lower shear stress SET. The performance of cromolyn sodium was superior to albuterol sulfate in the whole SETs dispersion study as was milled lactose monohydrate over sieved one. Concentration (0.5% vs 2%) as a numeric variable was not a determining factor on response.

CONCLUSIONS

- Significant differences in macroscopic aerodynamic dispersion and performance were correlated with differences in drug physicochemical properties, lactose grade, molecular interactions, interfacial chemistry, and nanotopography.
- The favorable interfacial and self-assembling properties of cromolyn sodium are reflected in its superior aerosol performance through decreased interparticulate interactions leading to aggregation.

ACKNOWLEDGEMENTS

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REFERENCE

Louey M.D., Van Oort M., and Hickey A.J., Standardized Entrainment Tubes for the Evaluation of Pharmaceutical Drug Powder Dispersion. *J. Aerosol Sci.* (2006) 37 (11) Nov: 1520-1531.