Comparative Dispersion Study of Dry Powder Aerosols of Albuterol Sulfate/Lactose Monohydrate and Disodium Cromoglycate/Lactose Monohydrate Delivered by Standardized Entrainment Tubes

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MOTIVATION

The dispersion studies using standardized entrainment tubes (SETSs) represent inhaler device independent screening tool of dry powder formulations (1). The well-defined and fully developed airflow conditions of SETs at given flow rate guarantee good reproducibility of drug deaggregation by overcoming the inter-particulate forces, thus good correlation of airflow conditions of SETs with the aerodynamic powder properties that are related to dispersion efficiency (2, 3).

OBJECTIVE

• To investigate in vitro aerosolization and particle deposition of albuterol sulfate and disodium cromoglycate with different lactose monohydrate carriers via SETs.

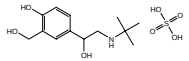
• To gain insight into the influencing formulation elements including drug, carrier, and concentration to the dispersion efficiency, under defined airflow condition.

To achieve aerosol performance prediction

MATERIAL

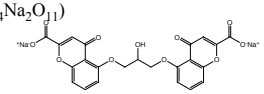
Pulmonary Drugs

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



Albuterol sulfate

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



Disodium cromoglycate

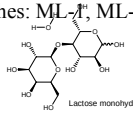
Respitose® Carriers

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

•Analysis led to selection of four batches;

• Sieved batches: SV-1, SV-2;

• Milled batches: ML-1*, ML-2.



Lactose monohydrate

METHODS

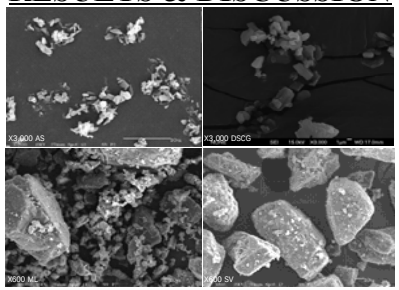
Attrition milling of drug, followed by geometric dilution and Turbula mixing with the lactose carriers. Malvern laser diffraction for volume particle size distribution (PSD). Particle morphology was characterized by scanning electron microscopy. Thermodynamic phase behavior, molecular interaction, and long range/short range order were evaluated by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) before and after blending. The blends were prepared at 2% (w/w) concentration.

Experimentally designed aerosolization was performed using twin-stage liquid impinger (TSLI) or Anderson cascade impactor (ACI) connected with a series of four SETs having aerodynamic diameters encompassing those of commercial DPIs. A set of statistical comparison of the data by 2^n full factorial design was performed to evaluate the effect of drugs, lactose monohydrate carriers, and SETs on the aerodynamic performance and delivery efficiency.

Aerosol Device	Reynold's number, Re	Shear Stress, τ_s, (N/m^2)	Power (Nm/s)	Pressure drop, ΔP, (N/m^2)
SET A*	18443	13.143	6.9194	6919.38
SET B*	13440	4.342	1.4915	1491.55
SET C*	11066	2.199	0.7470	747.01
SET D*	7720	0.624	0.1557	155.69

* Air flow parameters of SETs at Q = 60 L/min

RESULTS & DISCUSSION



Attrition-milled drug particle and Respitose® carrier distribution. Micronized drug particles were in the respirable size range with narrow unimodal particle size distribution. Both SV and ML were in the comparable size range but markedly different particle size distribution.

RESULTS & DISCUSSION

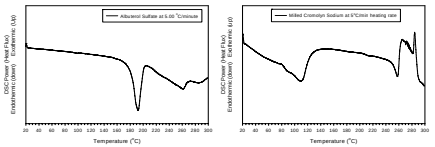
	Span	D_{10}	D_{50}	D_{90}
Alb#	0.26±0.09	3.20±0.06	3.59±0.13	4.13±0.40
Crom#	0.32±0.01	3.24±0.01	3.68±0.02	4.40±0.04
SV-1*	1.1-1.2	29.0	61.4	104.7
SV-2*	1.1-1.2	31.5	59.7	97.3
ML-1*	~3.1	4.20	54.6	174.9
ML-2*	~3.1	4.13	52.0	167.5

 # Mean and standard deviation, n = 2.

** The PSD of the 4 selected lactoses as supplied by the manufacturer.*

• DSC of micronized **AS**: T_m=193 °C Decompose over 210 °C

• DSC of micronized **DSCG**: Liquid crystalline thermogram revealing surfactant self-assembly phase behavior. ΔH is lower for milled sample than for unmilled sample-indicative of greater molecular disorder. No crystalline polymorphs



•Both ACI and TSLI dispersion data were in good agreement with each other. Only the data with solenoid switch on gave consistently increased fine particle faction (FPF) and decreased mass median aerodynamic diameter (MMAD) across the increasing pressure drop (ΔP), power, Reynold's number (Re) and shear stress (τ_s).

•For all studied formulations, DSCG/lactose monohydrate blends gave superior dispersion efficiency (higher FPF and lower MMAD) to AS/lactose monohydrate blends, indicating easier drug deaggregation of DSCG from lactose carrier. This may be attributed to differences in reduction of surface interfacial interactions (spontaneously reduction of surface energy of a polar surface in DSCG blends) or electrostatic matching of carrier and drug.

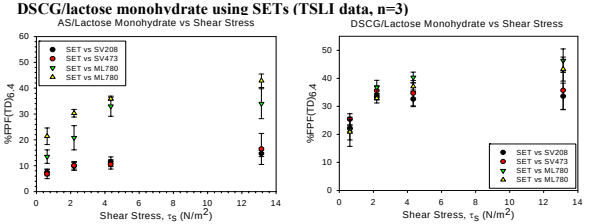
•SV lactose blends gave higher emitted dose (ED) than ML blends, because of the better flow properties of the former. The high shear SETs gave relatively lower ED than low shear ones, but the trend of ED difference became less obvious in the high shear condition.

•More importantly, the dispersion efficiency (higher FPF and lower MMAD) of ML blends

RESULTS & DISCUSSION

were superior to SV blends. This may be attributed to the presence of increased surface fines and surface rugosity observed in the ML lactose carriers.

Schematics of shear stress vs fine particle fraction of AS/lactose monohydrate and DSCG/lactose monohydrate using SETs (TSLI data, n=3)



Pairwise comparison of drugs, lactose carriers using highest shear SET-A and lowest shear SET-D (ACI data, n=2)

SET	Sample	ED (%)	$FPM_{6.5}$ (μg)	$FPM_{4.5}$ (μg)	$FPF_{6.5}$ (%)	$FPF_{4.5}$ (%)	MMAD (μm)
A	SV1+Alb	86.2 (3.5)	193.67(9.5)	168.455 (8.7)	18.0 (0.1)	15.6 (0)	1.99 (0.05)
A	SV2+Alb	92.9 (0.2)	250.86 (17.2)	228.285 (14.4)	27.2 (1.5)	24.7 (1.3)	1.86 (0.02)
D	ML1+Cro	78.7 (12.7)	198.44 (35.4)	131.775 (23.4)	20.3 (3.7)	13.5 (2.4)	3.21 (0.12)
D	ML2+Cro	89.7 (0)	233.52 (6.5)	152.64 (7.8)	24.5 (0.1)	16.0 (0.4)	3.27 (0.04)
A	ML1+Cro	82.1 (0.7)	446.23 (43.8)	327.62 (28.5)	46.1 (0.3)	33.9 (0.8)	2.92 (0.11)
A	ML2+Cro	82.7 (2.8)	474.53 (32.2)	351.605 (24.7)	48.9 (1.8)	36.2 (1.4)	2.88 (0.12)
D	SV1+Alb	87.2 (4.4)	128.73 (31.5)	106.85 (25.0)	11.5 (2.4)	9.6 (1.9)	1.99 (0.17)
D	SV2+Alb	89.7 (5.9)	178.23 (44.5)	145.04 (30.6)	17.1 (3.2)	13.9 (2.0)	2.27 (0.07)

CONCLUSIONS

• SETs are useful screening tools for formulation performance.

• Instantaneous actuation with solenoid switch was necessary for consistent dispersion characterization across different SETs.

• DSCG/lactose monohydrate formulations gave superior aerosol performance to AS/lactose monohydrateformulations, though interparticulate forces were previously reported to be stronger for pure carrier-free DSCG than AS(4).

• The favorable interfacial and self-assembling properties of cromolyn sodium are reflected in its superior aerosol performance through decreased interparticulate interactions leading to aggregation.

• In most cases, a trade-off between ED and FPF (or MMAD) was observed, but FPF and MMAD were more important factors in evaluating the dispersion efficiency.

ACKNOWLEDGEMENTS

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