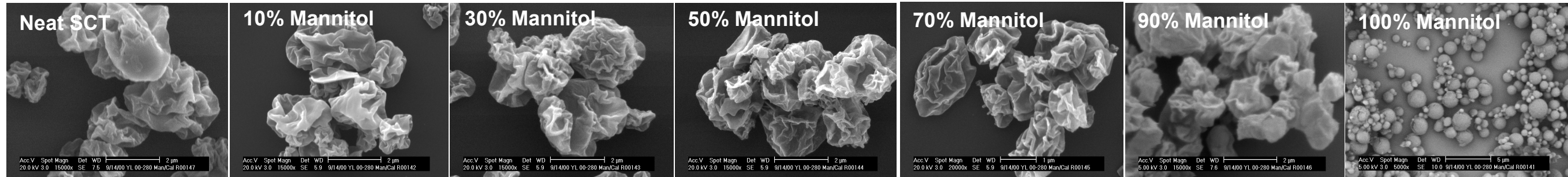


Effect of Bulk and Surface Properties on the Aerosol Performance of Dry Powders for Inhalation

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OBJECTIVES

To understand the role of bulk and surface properties on the aerosol performance of spray-dried powders for inhalation.

MATERIALS & METHODS

- Salmon calcitonin (SCT)/mannitol powders were produced with a Büchi 190 spray dryer.
- Surface concentration was determined by X-ray photoelectron spectroscopy (i.e., electron spectroscopy for chemical analysis or ESCA).
- Surface energies were measured by inverse gas chromatography (iGC).
- Emitted dose (ED), mass aerodynamic diameter (MMAD) and fine particle fraction (FPF) were measured by the Andersen cascade impaction method using a passive device (Dinkihaler™ made by Aventis).
- Particle size distribution and dispersion profiles were measured by Sympatec.
- Crystallinity was measured by Raman spectroscopy.

**Emitted Dose (ED)
and
Fine Particle Fraction (FPF)**

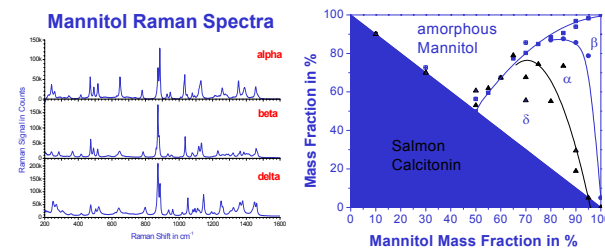
$$ED = 100 \frac{M_{filter}}{M_{blister}} \quad FPF = 100 \frac{M_{<3.3\mu m}}{M_{blister}}$$



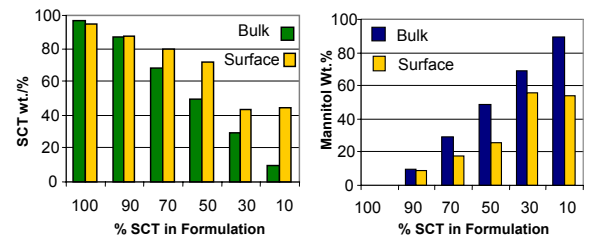
Dinkihaler™

RESULTS & DISCUSSION

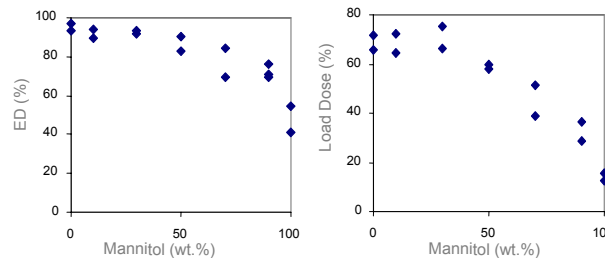
- 1 Formulation crystallinity is a function of mannitol concentration.



- 2 SCT preferentially accumulates at the surface of spray-dried particles, as measured by ESCA.

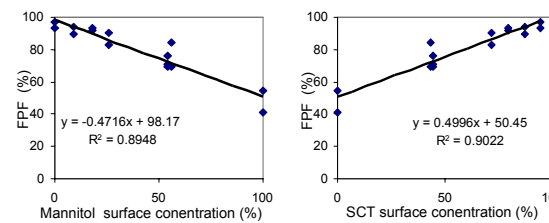


- 3 Emitted dose is improved as SCT concentration increases.

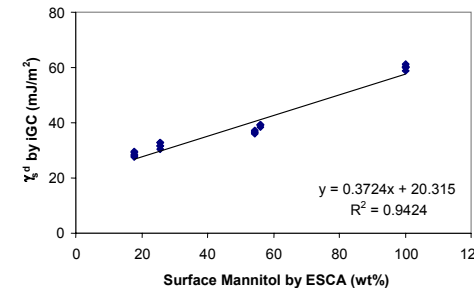


Measured in a Dinkihaler™ with a 10-mg capsule at a flow rate of 28.3 l/min. in a 'short-stack' ACI gravimetric assay. Load dose is the amount of fine particles in the aerosol divided by the powder loaded to the inhaler device for dispersion.

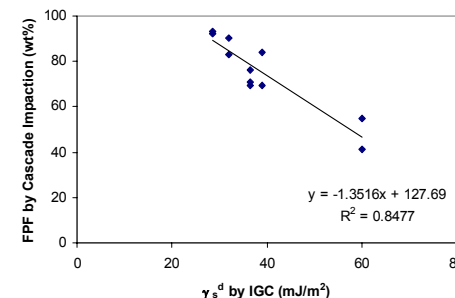
- 4 FPF correlates with the surface composition of spray-dried particles.



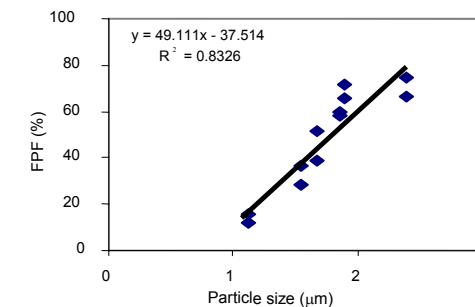
- 5 Surface enrichment by mannitol increases surface energy measured by iGC.



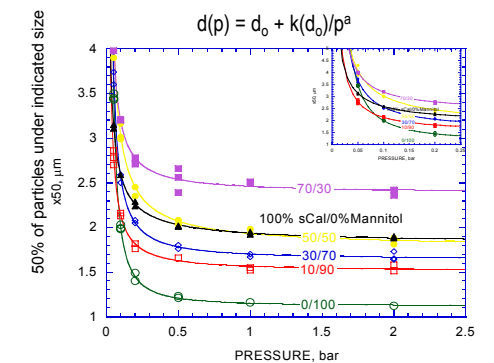
- 6 Powders with low surface energy exhibit improved FPF.



- 7 FPF is also a function of particle size, which depends on powder composition.



- 8 Particle cohesiveness of spray-dried particles is a strong function of composition as reflected by Sympatec dispersion profile.



DISCUSSION

- There is an inherent difficulty in isolating single effects since all properties are interdependent.
- Changes in composition induce changes in crystallinity, particle morphology and size distribution, as well as changes in surface composition and cohesiveness.
- Comparison of neat SCT and 10% mannitol (similar morphology, similar particle size distribution), reveal significant changes in surface energy, as measured by iGC and particle cohesiveness, estimated by the Sympatec dispersion profile.

CONCLUSIONS

- Surface composition does impact dispersion, based on the comparison of neat SCT and 10% mannitol formulations.
- Both iGC surface energy and Sympatec dispersion profile provide a "cohesiveness" measurement that correlates with FPF.
- Aerosol dispersion is a complex function of surface and bulk properties and highlights the importance of a systematic characterization of all powder properties through sophisticated methods.
- Dispersibility of spray-dried powders for inhalation is significantly improved by the presence of the peptide.

ACKNOWLEDGMENTS

The authors are grateful for the experimental work of Vathana Tep, Trixie Tan, Lisa Williams, Alex Mandel, and Yi Liang, all of Inhale Therapeutic Systems, Inc.