Investigation and Resolution of Particle Re-entrainment in NGI Analysis of a Spray Dried Formulation Emitted from a Dry Powder Inhaler

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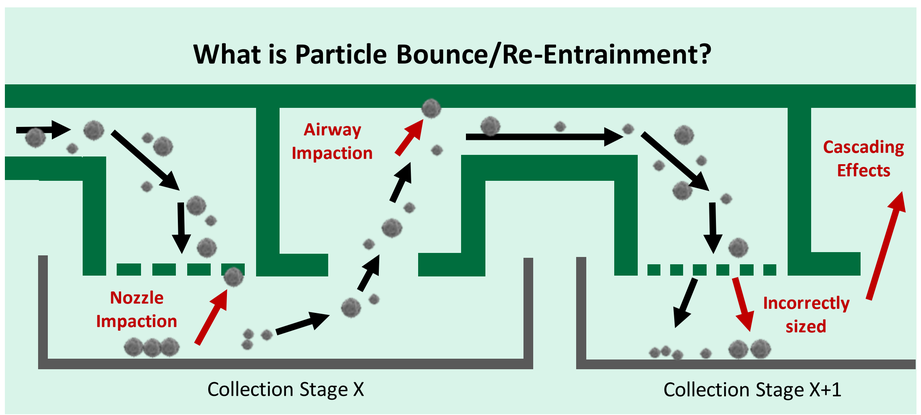
Introduction

Spray-dried particles were created as a lung cancer diagnostic, in concert with Owlstone's Breath Biopsy® technology. These formulations were engineered to have an almost entirely respirable particle size distribution.

Determination of aerodynamic particle size distribution (APSD) by Next Generation Pharmaceutical Impactor (NGI) relies on using an appropriate NGI stage coating to trap particles upon impact. Particle re-entrainment or 'bounce' occurs when stages become overloaded with fine material, exceeding the capture capacity of the coating material in use. This leads to inaccurate results as particles that 'bounce' are captured on later stages.

Many standard industry coating solutions were originally developed for carrier-based formulations,[1] where a limited percentage of the total formulation mass contributes to the respirable mass, as the API is aerodynamically separated from any carrier excipients. Engineered particles present a different challenge, as the whole mass of formulation may deposit in the respirable zone, potentially overloading individual stages.



Objectives

Industry-standard stage coatings suffer greatly from particle bounce when testing our engineered powders.

This study evaluated particle re-entrainment during NGI testing of engineered spray-dried particles using a low-viscosity, high-volume aqueous stage coating compared to industry-standard high-viscosity, thin film coating, with the goal of reducing or eliminating particle bounce.

Results

All the industry standard coatings performed comparably with significant particle bounce observed and a large post filter mass collection. This was even seen when the delivered mass was reduced from 40 to 10 mg.

Aqueous stage coating increased powder recovery by > 9% and narrowed the aerodynamic particle size distribution, aligning it more closely with observed geometric PSD, obtained by laser diffraction.

MMADs measured using the aqueous coating agreed across 10 - 40 mg delivered dose.

SEM images showed greatly reduced particle deposition on the Stage 8 MOC and post-filter, stages expected to only collect ultra-fines.

SEM images confirmed that particles collected in the MOC and post-filter are larger than expected for these deposition sites. No significant volume of fractured or < 500 nm diameter particles observed.

Conclusions

NGI stage coatings commonly used in the pharmaceutical industry showed significant particle bounce while testing the spray-dried powder, leading to inaccurate and imprecise APSD measurements. Signs of stage overloading even occurred at the modest capsule fill weight of 10 mg.

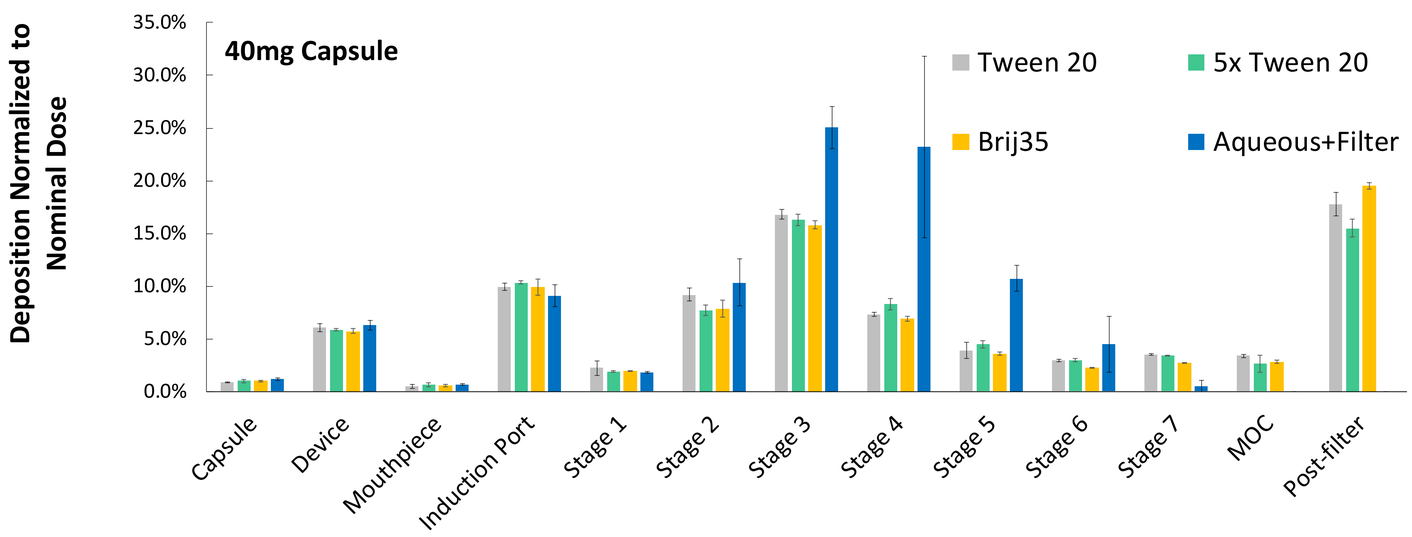
A low-viscosity, high volume aqueous stage coating method greatly reduced particle bounce, improving total recovery, accuracy and precision of the APSD with a range of doses delivered using a commercial DPI.

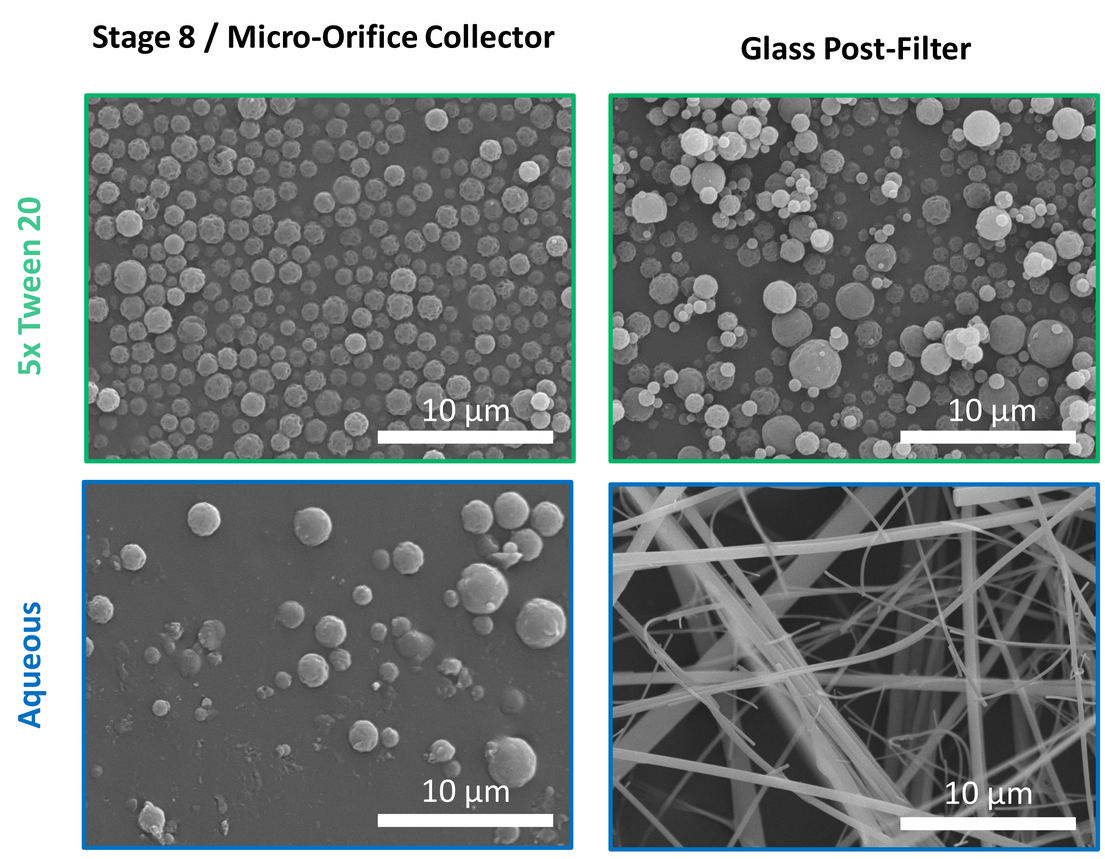
Methods

NGI testing of a spray-dried powder was completed with five different stage coating solutions using a commercially available inhalation device (BP RS01 High Resistance) and hand-filled capsules (10 or 40 mg powder), n=3. Stage pans coated with organic solutions were dried before actuation; when using aqueous solutions, the stage pans were coated immediately before actuation.[2] After dilution, powder deposition was quantified using HPLC-UV.

For one replicate of the 5x Tween20 and Aqueous coating solutions, the Stage 8/MOC and glass post-filter were sampled and imaged using Scanning Electron Microscopy.

Coating Solution	Concentration (g/L)	Solvent	Volume Added to Stage 2
Tween20	10	Ethanol	1 mL (10 mg dried)
5x Tween 20	50	Ethanol	1 mL (50 mg dried)
Brij 35/Glycerol	50/250	Ethanol	Minimal/poured off
Aqueous Tween 20	0.1	Water	1.5 mL
Aqueous Tween 20 + Filter	0.1	Water	1.5 mL





Coating Solution	Capsule Fill Weight (mg)	MMAD (µm)	GSD	FPF (%) (<5.0 µm)	Total Recovery (%)	Geometric PSD (By Laser Diffraction)	
						D(v 0.5) (µm)	Span
Tween 20	10	0.8 ± 0.2	4.5	83.3	88		
Aqueous	10	2.5 ± 0.0	1.5	75.2	103		
Tween 20	40	1.9 ± 0.1	2.4	75.2	85	1.6	1.4
5x Tween 20	40	2.0 ± 0.1	2.2	75.7	81		
Brij 35/glycerol	40	1.8 ± 0.1	2.5	86.7	81		
Aqueous + Filter	40	2.8 ± 0.1	1.6	78.0	94		

REFERENCES

1. Mitchell J: Practices of Coating Collection Surfaces of Cascade Impactors: A Survey of Members of the European Pharmaceutical Aerosol Group (EPAG), Drug Delivery to the Lungs 2003; XIV: pp 75-78.
2. Rissler J, Asking L, Kisbye Dreyer J: A Methodology to Study Impactor Particle Reentrainment and a Proposed Stage Coating for the NGI, J Aerosol Med Pulm Drug Deliv 2009; 22: pp 309-316.