A Performance Comparison of Popular Cup Coatings for the Prevention of Particle Bounce in Next Generation Impactors Using Imaging Techniques and HPLC Analysis

Kelsey Cairns[1], Frank Chambers[1] & Dr Lee Byrne[2]
1 - Inhalytic LTD, Discovery Park building 500, Sandwich, Kent, CT13 9EF, United Kingdom
2 - Canterbury Christ Church University, North Holmes Road, Canterbury, Kent, CT1 1QU, United Kingdom

Introduction

- Dry Powder Inhalers (DPIs) are a key platform for delivering inhaled therapies, and are favoured regarding sustainability and climate change concerns [5].
- Aerodynamic particle size distribution (APSD) is a key performance indicator for quality and efficacy of the aerosolized API and is determined using a cascade impactor [6].
- Control of particle bounce and re-entrainment is crucial to ensuring integrity of APSD when assessing DPI performance.
- Particle bounce is mitigated by applying viscous coatings to the stage cups and a wide range of substrate are currently in use [1, 2, 3].
- The 2003 EPAG survey catalogued commonly used substrates in the pharmaceutical industry [1.].
- Previous studies have evaluated coating performance [2, 3, 4]. However, these studies have not included a microscopic evaluation of coat uniformity when assessing impactor performance.
- This study combines a microscopic visual assessment of coating uniformity of a selection of substrates with quantitative impactor data.

Method

- Five popular coatings were selected from the 2003 EPAG survey, seen in Table 1.
- The coating substrates, plus an uncoated were assessed microscopically using
  - LEICA EZ4D microscope at 0.8x magnification.
  - LEICA DM500 at 40x magnification.

Coating Material	Solution Make up	Application method
Silicone oil	1% silicon oil in N-hexane	Let a thin layer evaporate in cup
Tween®	1% Tween in N-hexane	Let a thin layer evaporate in cup
Glycerol	Glycerol	Coat NGI Cup with a thin layer
Span™ 85	1% span in N-hexane	Let a thin layer evaporate in cup
Brij™ 35	5% Brij in water solution dissolved in 5g glycerol	Coat with a thin layer using a swab

Table 1 – Showing coatings evaluated in this study [1]

- APSD performance was assessed using salbutamol sulphate Accuhaler™ (n=3 per coating) using a Next Generation impactor (NGI), executed in accordance with USP <601>, using an air flow rate of 85 l/minute.
- HPLC analysis was undertaken using the proposed pharmacopeial monograph method for albuterol sulphate powder for inhalation [7], parameters summarised in Table 2.
- Data was processed to determine fine particle dose (FPD), fine particle fraction (FPF), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD), plotted and evaluated via ANOVA with post hoc Tukey tests.

Parameter	Specification
HPLC	Agilent 1100 System
Detector	VWD (G1314A)
Detector setting	UV 278
Column	Pursuit 5 µm C18 150 x 4.6 mm
Buffer (1L)	1.4g of Sodium Dodecyl Sulphate in 980 ML of water, 6.8 mL of phosphoric acid, adjusted with triethylamine to pH 2.5
Solution A	0.1% (v/v) phosphoric acid in HPLC water
Mobile Phase	Methanol and Buffer (45:55)
Diluent	Methanol and Solution A (45:55)
Standard solution	0.33 mg/mL of USP Albuterol Sulfate RS in Diluent

Table 2 –Materials and equipment used for the study, including the HPLC parameters, and make up of reagents.

- The data was also processed to produce APSD profiles.

Results and Discussion

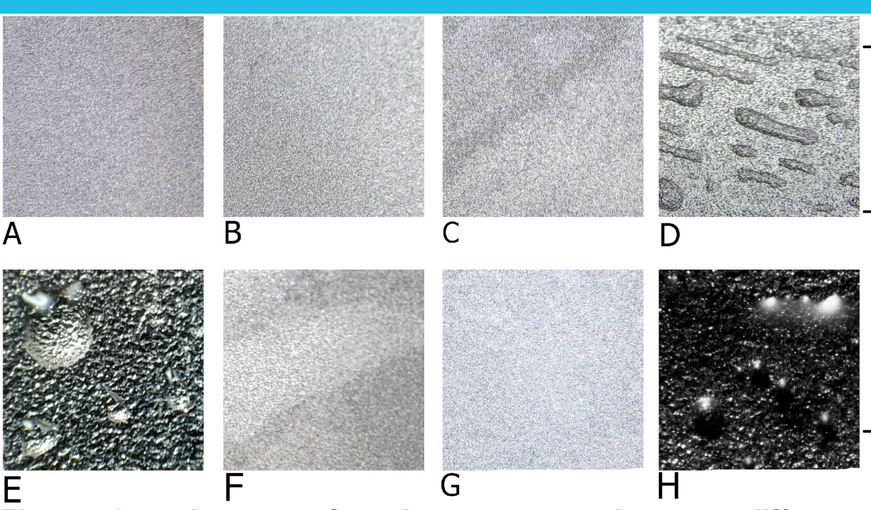

Figure 1 – Images of various cup coatings at different magnifications (Coating, description and magnification specified in Table 3).

Coating and Description	Magnification
(A) an uncoated, showing clear cup grain	0.8 X magnification
(B) silicone oil, showing clear cup grain	0.8 X magnification
(C) Tween®, showing clear cup grain	0.8 x magnification
(D) glycerol with the appearance of bubbles	0.8 x magnification
(E) glycerol, with the appearance of bubbles	40 x magnification
(F) spanTM, showing clear cup grain	0.8 X magnification
(G) brijTM, showing clear cup grain	0.8 x magnification
(H) brijTM, with the appearance of bubbles	40 x magnification

Table 3 – Summarising figure 1, specifying the coating, description and magnification.

- Non-water soluble coatings (B, C, F) appear similar with even coverage, and were tacky to the touch.
- The water soluble coatings were less uniform and were found to contain air bubbles.
- Mean APSD profiles are shown in Figure 2A.
- The coated cups exhibited consistent profiles, and prevented re-entrainment.
- The uncoated was a significant outlier, showing higher late stage deposition from stages 6 to 8, indicating re-entrainment, Figure 2A.
- A log probit was produced, and was used to calculate MMAD and GSD. A consistent gradient can be observed across the coated substrates, Figure 2B.
- Span™ was less effective than other coatings in controlling particle re-entrainment, and the uncoated deviated significantly from the trend.
- The FPD, GSD, and MMAD metrics for the coated cups compare well and differ significantly from the uncoated control data, Figure 3.
- FPF showed no significant difference between Brij™, Span™ and uncoated control.

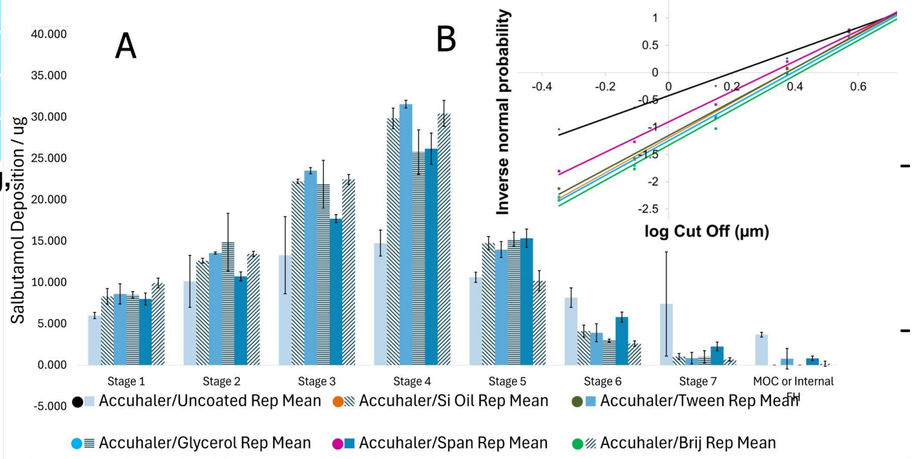

Figure 2 – A) Bar graph showing each coatings mean, in order of uncoated, silicon oi Tween®, glycerol, Span™ and Brij™ APSD profile by impactor stages, and B) Log probit plot showing the inverse normal probability of the means of each different cup coating including uncoated, silicon oil, Tween® glycerol, Span™ and Brij™.

- It is important to note that the low sample size (n=3) may affect the robustness of these observations.

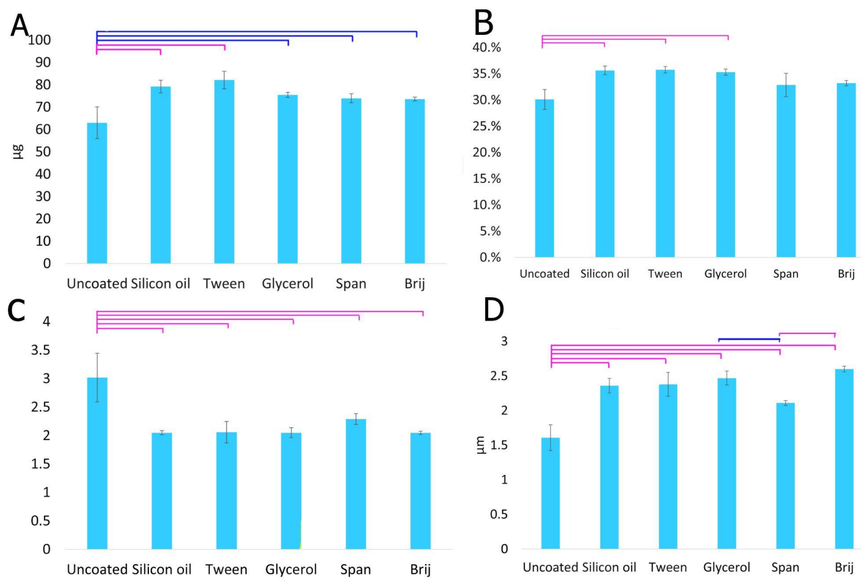

Figure 3 – Bar graphs showing, A - FPD, B - FPF, C - GSD, and D - MMAD. Brackets above showing any high significance, from the one-way ANOVA with post-hoc Tukey tests. The blue bars indicate P<0.05 and the purple bars indicate P<0.01.

CONCLUSION

- The primary aim of the study was to determine if there are any visual indicators of a coating's performance.
- All substrates effectively prevented salbutamol particle re-entrainment, regardless of visual coating uniformity.

The data did indicate that Span™ was slightly less effective when compared to glycerol, silicone oil, Brij™ and Tween®.

References
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