An assessment of the effect of vacuum crimping on dry powder filled pMDI cans.

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Introduction

Fluorinated gas propellants used in pressurized metered dose inhalers (pMDIs) generally have a high global warming potential (GWP).1,1-Difluroethane (P-152a) results in a >90% reduction in carbon footprint when compared with an equivalent HFA-134a formulation[1] although, flammability issues present some obstacles to overcome before adoption. Previous studies demonstrated an approach that mitigated flammability concerns at the formulation manufacturing stage. This was achieved by utilization of dry powder filling equipment to fill pMDIs, separating drug loading from propellant filling stages [2]. Vacuum crimping, a standard process used in pMDI manufacturing, ensures canisters are removed of air to avoid issues with hydraulic expansion and to improve fill consistency. Vacuum crimping in relation to dry fill processes and the subsequent impact on in-vitro performance was assessed in this extension of previous studies.

Methods and materials

Harro Höfligers Drum TT, a compact bench filling machine was used. The system comprises a dosing drum attached to a pneumatic unit controlling vacuum and compressed air.

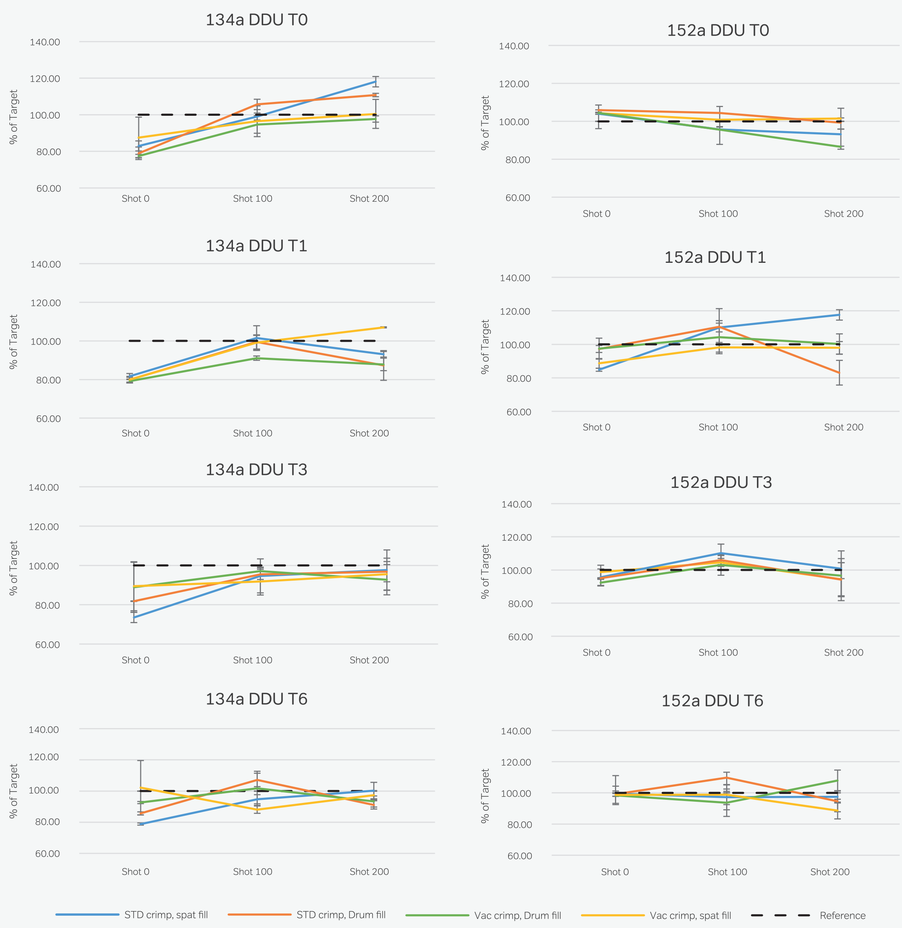
API weighed into 19mL aluminium cans was inhalation grade salbutamol sulphate. A Pamasol Vacuum Crimper (left) or 2016/100 laboratory plant (right) was used to crimp the cans.

Assay results

Total can assays were carried out to see whether vacuum crimping the cans resulted in a loss of API when compared to ambient crimped cans. Results showed there was no further mass loss as an effect of vacuum crimping for both propellants.

	% Recovery	
	152a	**134a**
Ambient crimp + Spatula fill	95.71	93.23
Ambient crimp + Drum fill	99.40	95.85
Vacuum crimp + Spatula fill	104.94	94.23
Vacuum crimp + Drum fill	99.02	98.59

Delivered dose uniformity (DDU)



Delivered dose throughout life against target for 0 to 6 months stability

- DDU results both 134a and 152a cans were within criteria, with no obvious improvement in performance seen from vacuum crimping the cans.
- On average 134a produced lower results (88 µg/mL ,86 µg/mL,90 µg/mL) at the beginning of can compared to 152a (113 µg/mL,99 µg/mL,103 µg/mL), this is consistent across all time points.
- To determine effect of crimping technique on DDU performance and to see if the population means were equal a two-sample t-test was performed.
- Grouping both filling methods across all shot numbers and timepoints resulted in a P-value of 0.271 indicating the vacuum process does not affect delivered dose performance through life.

Shot weights

152a	Average shot weight (mg)		
	BoL (RSD)	**MoL (RSD)**	**EoL (RSD)**
Spatula fill, Ambient crimp	0.115 (1.09)	0.113 (2.53)	0.113 (0.72)
Drum fill, Ambient crimp	0.115 (0.82)	0.114 (0.41)	0.113 (1.45)
Drum fill, Vac crimp	0.115 (1.08)	0.113 (1.45)	0.114 (2.18)
Spatula fill, Vac crimp	0.114 (2.19)	0.114 (1.45)	0.112 (0.73)

134a	Average shot weight (mg)		
	BoL (RSD)	**MoL (RSD)**	**EoL (RSD)**
Spatula fill, Ambient crimp	0.161 (2.92)	0.154 (5.45)	0.158 (3.43)
Drum fill, Ambient crimp	0.154 (2.81)	0.153 (1.11)	0.152 (0.31)
Drum fill, Vac crimp	0.158 (1.58)	0.155 (0)	0.153 (1.31)
Spatula fill, Vac crimp	0.158 (0.79)	0.152 (15.85)	0.151 (1.36)

Shot weights were not affected by either filling or crimping method across both propellants however RSD shows 134a was more variable. These observations are potentially due to the 152a optimized valve being used throughout the study.

APSD results: Fine particle fraction (FPF):

T0 produced an average FPF of at least 40% regardless of fill technique or propellant. Upon stability, FPF trends fluctuated however remained between 35% and 52% with no clear trending differences between fill technique.

	Fine particle fraction (%)			
152a	**T0**	**T1**	**T3**	**T6**
Ambient crimp, Hand fill	45.01	36.37	35.74	35.74
Ambient crimp, Drum fill	42.43	40.92	34.69	34.69
Vac crimp, Drum Fill	44.54	33.7	34.49	34.49
Vac Crimp, Hand fill	40.04	36.76	34.63	34.63

134a	**T0**	**T1**	**T3**	**T6**
Ambient crimp, Hand fill	42.43	46.61	47.77	33.60
Ambient crimp, Drum fill	39.87	38.66	38.76	40.77
Vac crimp, Drum Fill	42.39	45.99	44.11	47.22
Vac crimp, Hand fill	50.84	40.81	52.25	44.49

Stage deposition

Comparable results for 152a filled devices were produced across all variations, with a higher average result in stage 5 than stage 4.

Across all time points 134a showed a higher average in stage 5 then 152a resulting in a smaller MMAD (2.16µm v 2.62µm).

APSD performance for 0 to 6 months stability

Conclusions

Throughout the study, no observation regarding difference in performance due to crimping method or powder filling method was made. This work exemplifies that utilizing the standard manufacturing process used in industry of vacuum crimping after dry powder filling does not affect in-vitro performance for at least 6 months post manufacture.

References

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