Impact of Active Pharmaceutical Ingredient Span and the amount of Lactose Fines on Dry Powder Inhaler Formulation Performance

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) and Asthma are diseases for which the market is fast-growing, including several generations of products and an expanding base of players [1].
Besides conventional carrier-based Dry Powder Inhalers (DPI) formulations, novel formulations have been investigated to deliver drugs locally or systemically via the lungs [2]. In the case of carrier-based DPI formulations, the success of the formulation is mostly driven by factors such as APIs, lactose size, device and formulation processes. A thorough understanding of the impact of each factor can accelerate development. There have been studies investigating the impact of Active Pharmaceutical Ingredient (API) particle size on the aerodynamic particle size distribution (APSD) for metered dose inhalers [3] and the APSD impact of lactose fines in carrier-based DPI formulations [4]. However, the impact of API span and lactose fines on the APSD of the formulation has so far not been investigated.

RESEARCH GOAL

The objective of the present study was to increase the understanding of the impact of API span and lactose fines on product performance.

EXPERIMENTAL

Experiments		Fluticasone Propionate (FP) Span	Lactose Fines (% Particles below 10 µm)
Span	Low	4.4	9.7
	Mid	5.5	9.7
	High	8.9	9.7
Lactose fines	Low	5.5	6.8
	Mid	5.5	9.7
	High	5.5	12.8

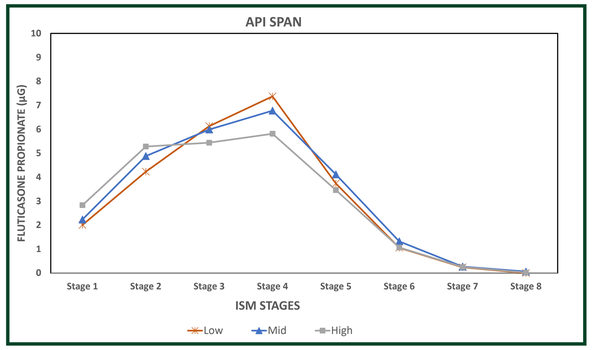
Fluticasone Propionate in HPMC capsules using RS01 Plastiape device was formulated.
API average D50 (µm) for the three Spans is 2.8.
For easier data evaluation, FP Span of 4.4, 5.5 and 8.9 will be referred to as low, mid and high span. Similarly, lactose fines 6.8, 9.7 and 12.8 will be referred to as low, mid and high lactose fines.

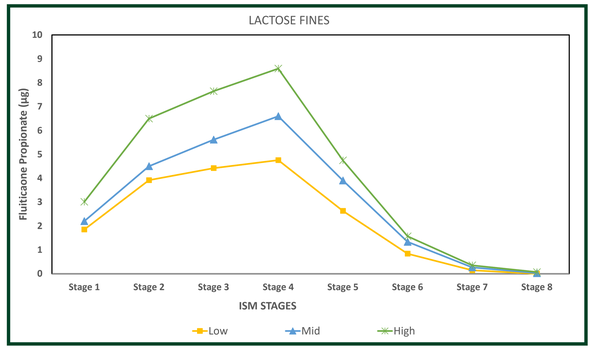
RESULTS – Assay, Content Uniformity and Delivered Dose

Parameters	Criteria	API - span			Lactose fines		
		Low	Mid	High	Low	Mid	High
Assay (n=3)	Mean (%) (95-105)	97.3	97.6	97.9	96.2	100.8	98.9
Content Uniformity (n=10)	Mean (%) (95-105)	99.9	97.7	97.7	96.2	98.3	100.1
	Acceptance value (Max. 15.0%)	9.5	6.0	5.9	12.6	4.6	3.4
UDD (n=10) % of Target	No criteria set	95.2	101.2	104.0	103.3	97.3	100.0

RESULTS – APSD

Parameters	Criteria	API - span			Lactose fines		
		Low	Mid	High	Low	Mid	High
Assay (n=3)	Mean (%) (95-105)	20.3	19.9	17.4	13.9	18.9	24.8
Content Uniformity (n=10)	Mean (%) (95-105)	24.8	25.6	24.2	18.6	24.4	32.5
	Acceptance value (Max. 15.0%)	2.8	2.8	3.1	3.1	2.8	2.9





CONCLUSION

Varying API span and amount of lactose fines showed an impact on APSD distribution using a capsule-based DPI. While API span impacts the aerosolized particle sized distribution of API over the NGI stages, lactose fines amount drives the concentration of fine particle dose or amount of drug deposition into the lungs, this behavior could be attributed to known theories such as active sites theory [4] or agglomeration theory [5]. Content uniformity, Drug Assay and Uniformity of delivered dose were not significantly affected by the change of API span or lactose fines concentration. Full factorial Design of experiments using API span and lactose fines, are planned which could highlight the combined effects of both.

REFERENCES

1. Allied Market research: COPD and Asthma Devices market [**https://www.alliedmarketresearch.com/COPD-asthma-devices-market**] Accessed January 23, 2023.
2. Berry J, Kline L, Sherwood J, Chaudhry S, Obenauer-Kutner L Hart J, Sequeira J: Influence of the size of micronized active pharmaceutical ingredient on the aerody namic particle size and stability of a metered dose inhaler. *Drug Dev Ind Pharm* 2004, 30 (7), 705-14.
3. Kinnunen H, Hebbink G, Peters H, Huck D, Makein L, Price R: Extrinsic lactose fines improve dry powder inhaler formulation performance of a cohesive batch of budesonide via agglomerate formation and consequential co-deposition. *International Journal of Pharmaceutics* 2015, Vol 478, Issue 1, 53-59.
4. J. A. Hersey. Ordered mixing: A new concept in powder mixing practice. *Powder Technology. Volume 11, Issue 1, January–February 1975, Pages 41-44*
5. Gerald A. Hebbink, Maarten Jaspers, Harry J. W. Peters, Bastiaan H. J. Dickhoff: Recent developments in lactose blend formulations for carrier-based dry powder inhalation. A*dvance Drug Delivery Reviews 189 (2022) 114527.*

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