Understanding the affect of DPI device and lactose type on the output from a device

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Summary

Dry powder device are more complicated to design and develop then pMDI and Nasal devices. During the development process there are three components to optimise for a device to work correctly, device, API and lactose. Each component has a range of complex interaction which impact on how the final device will perform. On the device a designer / developer will consider a range of issues such as, type of material, how the dose will be delivered, how to maintain the uniformity and will the device be a single dose or multi dose, and also need to be easy to use. API and lactose performance is subject to, particle size, particle shape, type of production, mode of blending, how they fluidise and breakup to release the API, all play a role in the optimisation of the final product. The aim of the paper was to assess, change in the output from a Easyhaler® standard reservoir DPI device with 3 types of lactose, *Respitose® SV003, Respitose® ML001 and Lactohale® 300*. The following parameters were measured, plume angle, event duration and intensity profile of lactose from the device. The results show, for plume angle and event duration there was no significant difference between *Respitose® SV003* and *Respitose® ML001*. The results for *Lactohale® 300* are significantly different. The intensity profile results provide some insight in to how the material flows from the device and the release profile for each combination. *Lactohale® 300* profile is different, to that of *Respitose® SV003* and *Respitose® ML001*, with a slow decay over the event. This may in part be due to the small size range (D50 <5um) and the mechanisims involved in the fluidisation and agglomerate breakup of the powder from the device.

Introduction

The design and development of a dry powder platform is a complex maze of interaction between the device, the carrier (lactose) and API. For each components there are a unique range of variable to consider, for the device, a designer / developer will need to consider the mode of release, easy of use, type of material, and mode of controlling the dose uniformity either capsule, reservoir, or blister device. For the carrier (lactose), the method of manufacture, particle size, particle shape, type of release and the interaction with API and blending process need consideration. For API, the physical properties will affect the API release from the lactose. Are there any reactions between the different components, which prevent the API from releasing? In the following paper we consider the impact of lactose type on the output from a standard DPI reservoir device. The *"Easyhaler®"* from Orion Pharma was selected, which delivered a dose of 70mg. Three Lactose types (see Table 1) produced by DFE Pharma were selected, Respitose® SV003, Respitose® ML001 and Lactohale® 300.

The aim of the study is evaluate the effect of three lactose powders on the output from *"Easyhaler®"* DPI device. Tests evaluate plume angle, spray pattern, event duration and output intensity profile from the DPI device.

Figure 1. EnVision DPI System

Methodology;

The *EnVision* DPI system (Figure 1), provides fixed hardware configuration around the DPI test chamber for the high speed camera and short pulsed *FireFLY* laser. This allows the EnVision system to capture and illuminate the powder as it was evacuated from the *"Easyhaler®"* device. The imaging and data collection were carried out with reference to FDA guidance documents[2 & 3].
A vacuum pump connected through a solenoid valve operating at 50l/min extracted the powder from the *"Easyhaler®"* Dry Powder device. The event started when the solenoid was triggered, at the same time the imaging system captured images of the transient powder flow event.

Table 1
Lactose selected for testing in Easyhale® DPI reservoir device

Powder Type	Process	Particle Size Range (um)		
		d_{10}	d_{50}	d_{90}
Respitose® SV003	Sieved	26	56	86
Respitose® ML001	Milled	4	49	169
Lactohale® LH 300	Micronized		3	7

A fine light sheet was used to dissect the flow, from the *"Easyhaler®"* device. In 1992 Masahiko Nishida, et al[4] used an Oxford Lasers CVL laser system to show how laser light sheets could be utilised to obtain information on the plume angle and spray pattern in the automotive sector. The camera captures images at 500Hz, as the particles move through the light sheet. A DPI test chamber allows the EnVision camera system to visualise the flow of powder from the *"Easyhaler®"* device, of either the plume angle or spray pattern. EnVision software is used to analysis the images to obtain the required information.

Results and Discussion

The plume angle varies from 15.8 degrees to 21.0 degrees across the 3 powders reference Table 1. Comparison between SV003 and ML001 show no statistical difference in the plume angle (Figure 2). When SV003 & ML001 are compared with LH300, the results show a significantly different, with a 32.6% increase in the plume angle (Figure 2).

Table 2
Plume angle & duration results from a* Easyhaler® *device with 3 powders

Lactose Type	Plume Angle (°)	Plume Width at		Plume Length	Duration Time
		6 cm	3 cm	cm	ms
SV003	15.89	2.15	1.31	16.12	82.67
ML001	16.42	2.33	1.48	16.77	90.00
LH300	21.08	2.85	1.49	15.91	118.00

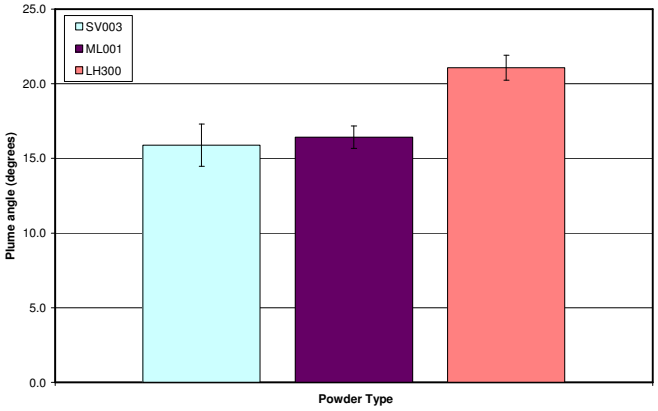

Figure 2 Plume angle results

Results following event duration (Table 2) show similar trend to the plume angle. No significant difference between SV003 & ML001 with duration time of 82 & 92ms respectively (Figure 3). Results For LH300 are significant different to SV003 & ML001 with a 35.3% increase in duration up to 118ms.

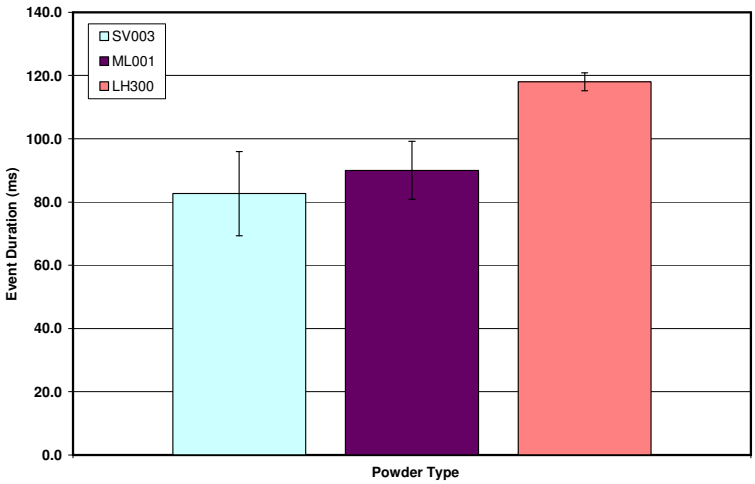

Figure 3 Event Duration (ms)

Results in Table 3, show spray pattern details at 3cm and 6cm from the device exit. At 3cm the ovality ratio shows variation between 1.47 and 1.73 for the 3 lactose types. At 6cm the variation ranges from 1.62 and 1.69.

Table 3
Spray Pattern characteristics from a* Easyhaler® *device with 3 powders

Lactose Type	Spray Pattern at 3cm				Spray Pattern at 6cm			
	Area (cm^2)	Dmax (cm)	Dmin (cm)	Ovality Ratio	Area (cm^2)	Dmax (cm)	Dmin (cm)	Ovality Ratio
SV003	0.95	1.49	0.84	1.73	1.27	1.68	1.04	1.62
ML001	1.54	1.70	1.14	1.47	1.98	2.09	1.29	1.69
LH300	1.35	1.76	1.03	1.73	1.92	2.28	1.37	1.66

In Figure 4, results show the intensity profiles information from output of the device. Results show similar trend as plume angle and event duration. The Respitose® SV003 sieved lactose results show intensity peak of 0.049 and decrease rapidly. The Respitose® ML001 milled lactose shows a delay in the initial lactose release of 0.004s and then increases to a peak of 0.040 at the similar rate as the SV003 lactose. For the Lactohale® 300 the initial rise of the intensity / flow of lactose from the device from 0 to 0.0344 @ 0.020s is the similar to SV003. As the event continues the output intensity from the LH300 decreases slowly over the remaining time period of the event.

The intensity profiles in figure 4 also provide information on release of the lactose from the device. For Respitose® SV003, 75% of the lactose was released from the device in 0.045s. For Respitose® ML001, 75% of the lactose was released from the device in 0.061s. For Lactohale® 300, 75% of the lactose was released from the device in 0.068s. Results for LH300 also show, after reaching the peak intensity, the flow decreases, but appears to vary up and down over the remaining time period. Is this due to the performance of the lactose or a combination of the device and flow dynamics required to fluidizes the lactose.

Respitose® SV003 and Respitose® ML001 show similar D50 particle size range, 56um and 49um respectively. The Respitose® SV003 has a norrow size range between 25um to 86um. Respitose® ML001 has a wide size range between 4um and 169um. When examined under actuation both powders behave differently, for Respitose® SV003 a free flowing lactose, fluidization happens when individual lactose particle are eroded from the surface of the powder bed, for Respitose® ML001, the increased number of small particle increases the cohesive properties of the lactose to produce agglomerates, the powder is lifted up into the airflow, interactions between the agglomerates / agglomerates and agglomerates / device device result in break up and release of the active indridgent.

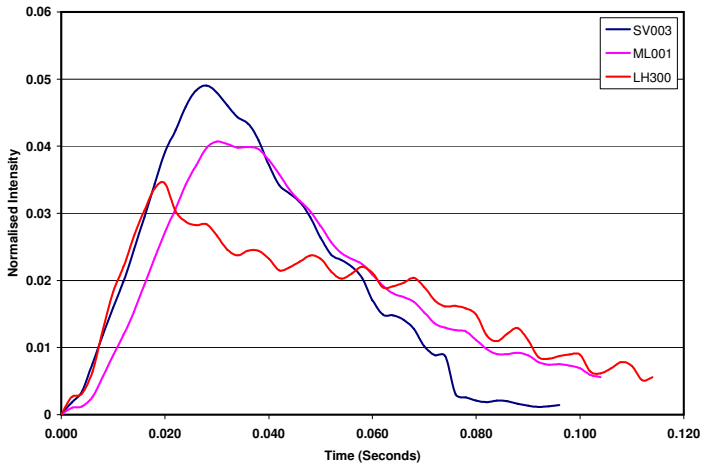

Figure 4 Intensity profile for SV003, ML001 & LH300 at the device exit

The Lactohale® 300, is a micronized lactose, very narrow size range with D50 of 3um. The Lactohale® 300 is very cohesive lactose. When a powder bed of Lactohale® 300 is excited, it forms very large agglomerates that breakup through airflow interactions and impaction. The extream stickness of the Lactohale® 300, could results in some adhesion of the lactose to the *"Easyhaler®"* device. This adhesion would in part explain the variability in the output profile from the *"Easyhaler®"* device.

Conclusion

The plume angle and event duration show no significant difference between the Respitose® SV003 and Respitose® ML001 lactose. Lactohale® 300 lactose shows significant differences between the plume angle and event duration. Lactohale® 300 lactose shows more than 35% increase in plume angle and event duration. The release profile for Lactohale® 300 has a lower peak intensity than Respitose® SV003 and Respitose® ML001, combined with a slower rate of decay which is related to the mechanism of fluidization and to a range of properties, such as reduced particle size, powder forms large agglomerates, miss match between device material properties and lactose resulting in electrostatic effects, resulting In slower release of the powder from the reservoir device.

References

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