Enhanced engineered formulations in dry powder inhalers for high dose lung delivery

Susana Saldanha*, Luís Sousa, Eunice Costa

R&D, Hovione FarmaCiência SA, Lumiar, 1649-038, Portugal

*ssaldanha@hovione.com

BACKGROUND

Acute and/or emergency indications

- **High payloads of pharmaceutical compounds**
- **Single use disposable devices**
  - Antibiotics
  - Antivirals
  - Vaccines

COMPOSITE ENGINEERED PARTICLES

- Efficient formulation for delivering high drug loads
- Inclusion of force control agents and/or particle morphology optimization to maximize dispersion

- Low bulk density
- Challenges in downstream processing: long filling process times, high dose variability
- Challenges in powder dispersion in high resistance devices (e.g. reservoir devices)

For delivering high dosages, considering the composite powders characteristics and the type of devices (reservoir devices), the DPI developer is faced with several challenges to be addressed:

- **Lack of processability**: accurately filling these powders into devices for inhalation
- **Challenges in aerodynamic particle size distribution from reservoir-based devices** due to turbulence driven dispersion mechanisms in combination with high cohesive-adhesive powder properties of high dose formulations.

MATERIALS & METHODS

COMPOSITE ACTIVE PARTICLES

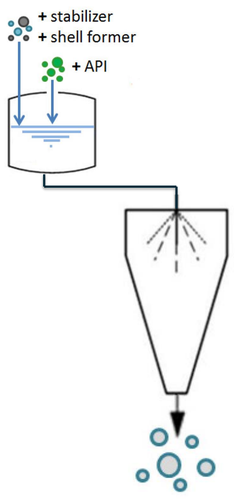
API (50% w/w)
Leucine (25% w/w)
Trehalose (25% w/w)

CARRIER-BASED FORMULATION

Micronized API (25% w/w)
Lactose monohydrate (75% w/w)

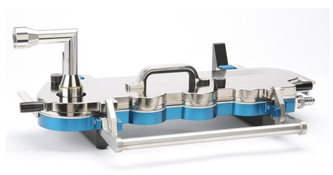
COMPOSITE COMBO

Composite active particles (50% w/w)
Lactose monohydrate (50% w/w)



- Single use disposable device;
- Reservoir-type;
- Two reservoirs per device.

Active ingredient particles (Composite particles or micronized API) were characterized for Particle size distribution (PSD) using a Mastersizer 3000 from Malvern Instruments.



The products' performance was evaluated based on USP <601> using a Next Generation Impactor (NGI). **TwinCaps MAX at 36 L/min, 4kPa**

RESULTS AND DISCUSSION

The aerodynamic performance data obtained is presented in Table 1 and Figure 1:

Emitted Dose:

- Emitted Dose of the composite active particles alone (A) is 2.5 mg opposing to the composite blend (B) that is 7.9 mg.
- The majority of the powder remained inside the device on the composite active particles alone formulation (6.5 mg).
- In case of the **composite blend**, just a few micrograms of powder were left inside the device (0.8 mg) after actuation.

Fine Particle Dose & Fine Particle fraction:

- Fine particle dose (FPD) of the **composite blend** is much higher than the composite active particles alone, 3.9 mg and 0.3 mg, respectively.
- FPD is higher even compared with a common carrier-based blend having the active ingredient micronized.

Table 1. Formulations composition and aPSD data

		A: Composite particles	B: Composite Blend	C: Carrier-based blend
Active material		Composite API API:LEU:TRE (50:25:25)		Micronized API (25%)
Active material particle size distribution (PSD)				
	Dv90	4.3		5.7
	Dv50	1.7		2.1
	Dv10	0.6		0.6
Composition				
Composition	Composite particles	100%	50%	0%
	Lactose monohydrate	-	50%	75%
Filling per reservoir	mg	15.5	31	31
Dose per reservoir	mg	9.0*	9.0*	7.75
Analytical results				
ED	mg/device reservoir	2.5	7.9	5.7
FPD	mg/device reservoir	0.3	3.9	1.8
FPF_{ED}	%	12.0	49.4	31.6
MMAD	µm	4.2	2.9	3.3
GSD		1.8	1.9	2.0
Material in the device	mg/device reservoir	6.5	0.8	1.7

*Dose corrected according composite particles Assay %.

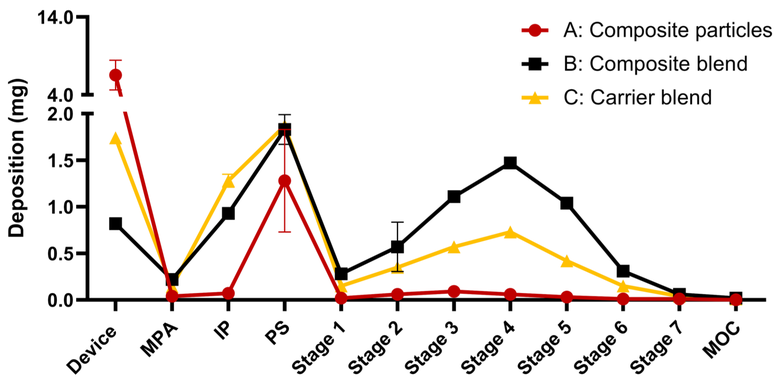


Figure 1. NGI data of the formulations tested

The flow induced turbulent kinetic energy and shear stresses within the reservoir device was insufficient to fluidize the composite active particles and promote its emission. The powder dispersion process in a DPI is highly complex and involves several physical mechanisms. Reservoir-based devices, such as the single-dose devices, typically rely only on the turbulence generated by the airflow to aerosolize the powder, opposing to capsule based devices that benefit from the movements of the capsule, like vibration, rotation and shaking. This might challenge the efficiency in aerosolization and delivery of dry powder formulations, especially in the high drug loads end. *In vivo* this effect might be even more remarkable especially for conditions where the breath flowrate is compromised.

The **composite blend** results show that by adding a fluidizing agent (such as Lactose monohydrate) both the emitted dose and fine particle dose are enhanced and, consequently, the dose that reaches the lungs.

CONCLUSION

Reservoir-based devices such as TwinCaps® and TwinMax DPIs, are suitable for delivering not only low dosage formulations, but also high dosage formulations, in an efficient manner.

The use of a coarse carrier as a fluidizer was an enabler in the composite blend (B).

The formulation developed solved the processability issues during filling associated with the high cohesiveness of the spray dried composite active particles.

The formulation-device combination presents particular interest in high drug load inhalable powders or other API that need composite particles for overcoming the solubility and high drug load challenges.

1. Sibum et al F: *Challenges for pulmonary delivery of high powder doses;* ***2.*** Ye Y, Ma Y, Zhu J, *The future of dry powder inhaled therapy: Promising or Discouraging for systemic disorders?;* ***3.*** Berkenfeld K et al: *Devices for Dry Powder Drug Delivery to the Lung****; 4.*** Ventura J, Villax P, *Dry Powder Inhalers: towards effective, affordable, sustainable respiratory healthcare;* ***5.*** Cruz R et al, *Carrier-based Formulation Dry Powder Inhalers Using TwinCaps®: Aerodynamic Particle Size Distribution and Laser Diffraction Analysis for a Typical Patient Population Peak Inspiratory Flow Rate Range****; 6.*** Alhajj N, O'Reilly N J, Cathcart H, *Designing enhanced spray dried particles for inhalation: A review of the impact of excipients and processing parameters on particle properties;* ***7.*** Moura C, Neves F, Costa E*: Optimized Composite Particles for API-independent Formulations with Enhanced Performance*. (Abstract); **8.** Groß R et al, *State of the Art in Capsule-Based Dry Powder Inhalers: Deagglomeration Techniques and the Consequences for Formulation Aerosolization*