Evaluation of Performance of Dry Powder Inhaler Formulations by Laser Diffraction

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Introduction

One of the most challenging aspects of drug delivery to the lungs is the cohesiveness of micronized particles, which impacts powder dispersion and, subsequently, aerodynamic performance.

Because the dispersibility of powders greatly impacts aerodynamic performance it is important to characterize these powders. Laser diffraction (dry dispersion) has previously been utilized to characterize the dispersibility of agglomerates of drug and an excipient (lactose) [1] and attempted to predict correlations with the aerodynamic performance results obtained from cascade impaction testing [2]. However, the methodology needs validation with cascade impaction results and assessment of the dispersion pressure and cut-off particle size that best fits the product in question.

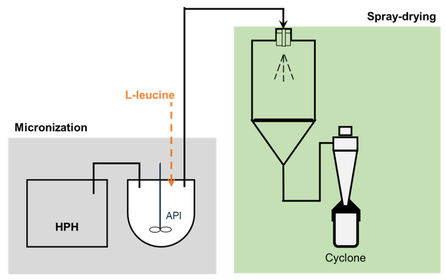
Therefore, we propose a new laser diffraction methodology (dry dispersion) to evaluate the aggregation state and powder dispersibility of Dry Powder Inhaler (DPI) formulations, which correlates with performance. The rate of de-agglomeration of powders is determined by Sympatec, as a function of dispersion pressure, and used to establish correlations with performance for different formulations and types of formulations.

Materials and Methods

1. Materials

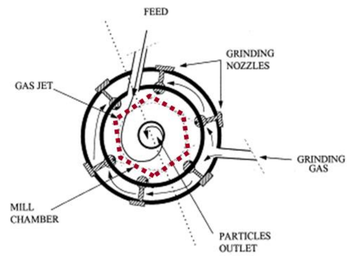
Composite particles

- Process: Wet Polishing (water)
- High-pressure homogenizer for micronization
- Spray drying of API suspensions with leucine
- Particles containing 0; 5 and 15% leucine
- PSD (micronized API): Dv90 of 4.5 µm



Co-milled formulations

- 2 diferent excipientes, 1 API
- Low shear mixing followed by jet milling
- 3 blends (89-99% w/w API content)
- PSD (micronized API): Dv90 4-6 µm



2. Methods

Aerodynamic performance evaluation (by NGI)

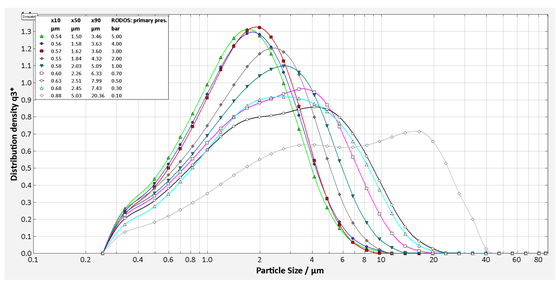
- PowdAir® dry powder inhaler
- 30 mg capsules
- 4 kPa for 4 L volume (n=3)
- Controlled conditions (20-25 ºC & 40-50% RH)
- Quantification by HPLC
- ED and FPF calculated with CITDAS.

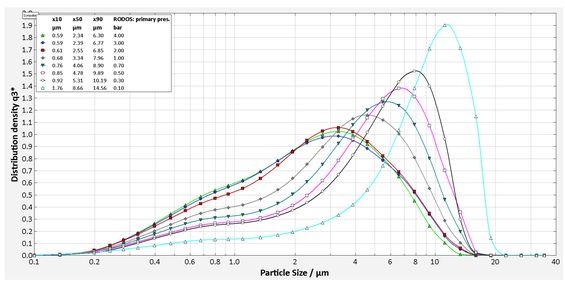
Particle size distribution determination (Sympatec)

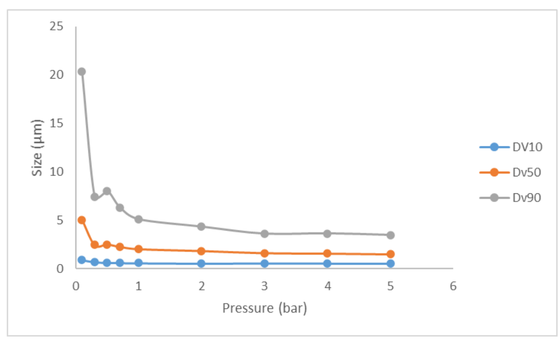
- *Helos/Rodos/Aspiros (Sympatec)*
- *R2 lens (composite particles) and R1 lens (co-milled formulations).*
- *Feed velocity: 50 mm/s*
- *Pressure: 0.1, 0.3, 0.5, 0.7, 1, 2, 3 and 4 bar (also 5 bar for composite particles).*

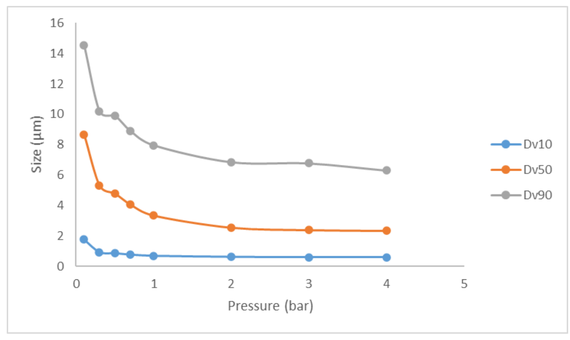
Results and Discussion

Determination of the rate of de-agglomeration

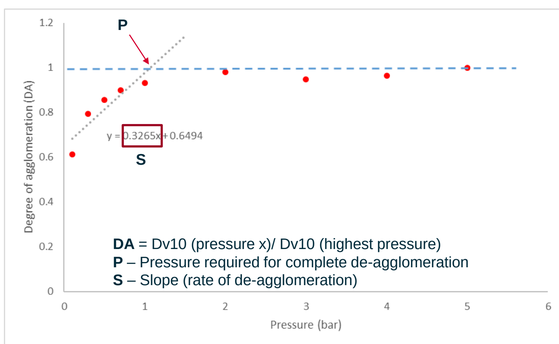






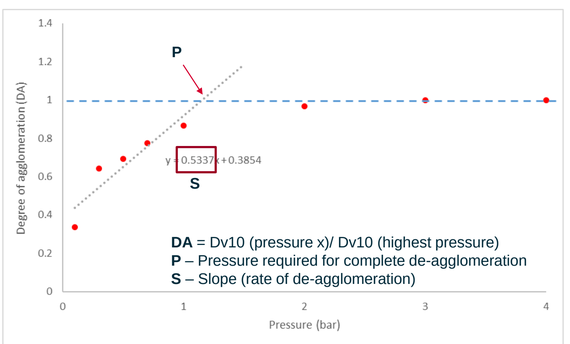


For Dv10



DA = Dv10 (pressure x)/ Dv10 (highest pressure)
P – Pressure required for complete de-agglomeration
S – Slope (rate of de-agglomeration)

For Dv10



DA = Dv10 (pressure x)/ Dv10 (highest pressure)
P – Pressure required for complete de-agglomeration
S – Slope (rate of de-agglomeration)

Figure 1. Sympatec pressure curve data (Composite particles – 10% leucine).

Figure 2. Sympatec pressure curve data (Co-milling Blend 1).

Correlation of de-agglomeration parameters with aerodynamic performance

Composite particles (Leucine)

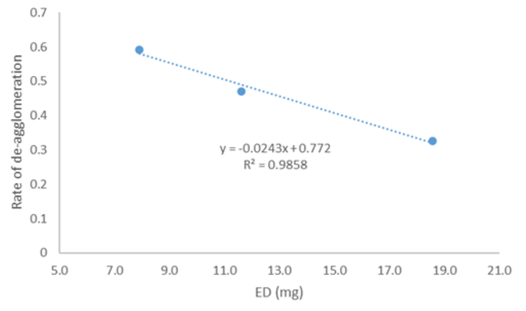


Figure 3 - Emitted dose vs rate of de-aggregation, calculated based on Dv10 results.

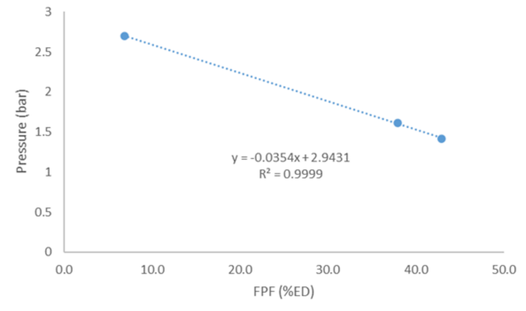


Figure 4 – Fine particle fraction vs pressure required for complete de-aggregation, calculated based on Dv90 results.

- Good linear correlations between the emitted dose and the rate of de-aggregation.

Co-milling formulations

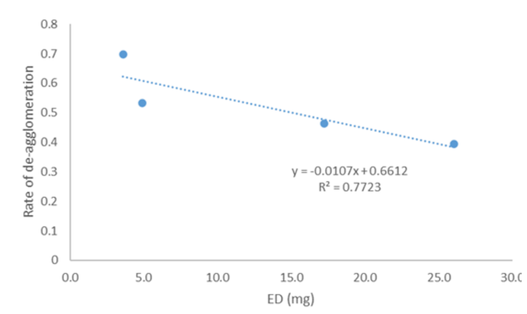


Figure 5 - Emitted dose vs rate of de-aggregation, calculated based on Dv10 results.

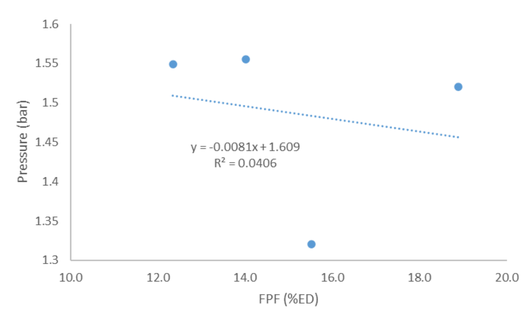


Figure 6 – Fine particle fraction vs pressure required for complete de-aggregation, calculated based on Dv90 results.

- Tendency for increase in ED with lower de-agglomeration rates.
- No linear correlation nor tendencies were found between de-agglomeration and FPF, for co-milling formulations (short FPF range 12.3-18.9 %).

Conclusions

- The rate of de-aggregation and the pressure required for complete de-aggregation seem to correlate well with the ED and FPF, respectively.
- The correlations found must be further demonstrated with a larger number and type of formulations to allow more data points available for the linear regressions performed.
- This methodology will be useful for ranking powder formulations based on their dispersibility, in early-stage formulation screening. Despite its potential, the methodology does not intend to predict aerodynamic performance since that is dependent on many other factors such as the type and resistance of the device, capsule, air flow etc.

[1] Jaffari S, Forbes B, Collins E, Barlow DJ, Martin GP, Murnane D. *Rapid characterisation of the inherent dispersibility of respirable powders using dry dispersion laser diffraction*. Int J Pharm 2013;447:124–31.

[2] Arevalo F, Tignor SE, Sellers S. *Using Dry Dispersion Laser Diffraction to Assess Strength and Dispersibility in Spheronized Agglomerate Formulations*. RDD 2022 Respiratory Drug Delivery, Omni Orlando ChampionsGate, Florida: RDD Online; 2022, p. 273–6.