GRANUTOOLS™ POWDER FLOW CHARACTERIZATION

POWDER FLOW, COHESION, PACKING AND ELECTRIFICATION

Evaluation of Different Powder Characterization Techniques for DPI Performance in Capsule-based Inhalers

Salvatore Pillitteri[1], Joana T. Pinto[2], Sarah Zellnitz-Neugebauer[2], Aurélien Neveu[1], Filip Francqui[1]

[1]Granutools, Rue Jean Lambert Defrêne 107, Awans, 4340, Belgium

[2]Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 13, 8010 Graz, Austria

INTRODUCTION

Dry Powder Inhalers (DPIs) are used to orally deliver drug powders to the lungs to treat respiratory diseases. While extensively employed, the active pharmaceutical ingredient (API) has often insufficient aerosolization properties and a poor flowability that makes handling and delivery difficult [1,2]. Moreover, the API is often used in very small quantities. For these reasons, inhalable API particles are usually mixed with larger excipient ones, that act as carriers for the drug [3].

Generally, lactose powders are chosen as carrier excipients. The performance of the DPI can be very different depending on the selected grade. In-vitro, the aerosolization performance of these different combinations can be evaluated with the fine particle fraction (FPF) and the fine particle mass (FPM) of the API via impaction. However, these evaluations can be cumbersome and take extensive amounts of time. Thus, characterization of bulk powder properties can be essential when preselecting potential carrier candidates for DPI.

In this work we characterized three powder blends of salbutamol sulphate (SS) with distinct lactose grades using tapped density (GranuPack, Granutools) and rotating drum (GranuDrum, Granutools) methods.

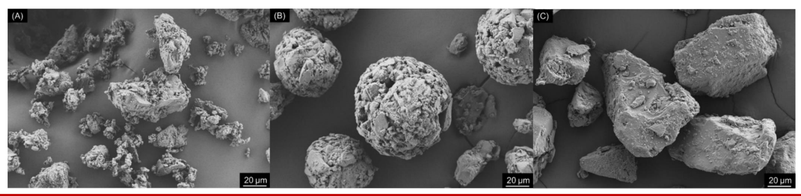
Material

Three binary powder blends with a different lactose grade:

- Duralac® H
- Flowlac® 90 (both MEGGLE GmbH & Co. KG, Germany)
- Respitose® SV003 (DFE Pharma, Germany)

mixed with 2% in weight of micronized SS ($D_{V0.5}$ = 1.43 ± 0.04 µm) (see [2] for more information about the procedure)

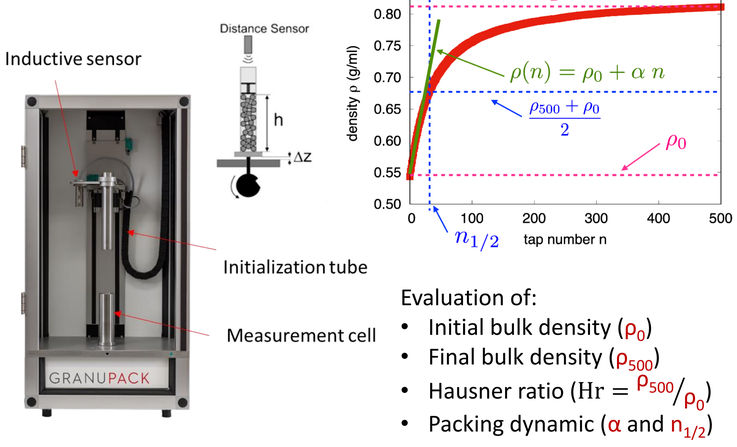
Name	D_{50} (µm)	Fraction < 10 µm (%)
DuraLac® H	52.89 ± 7.10	13.48 ± 1.76
Respitose® SV003	60.26 ± 3.76	3.34 ± 0.07
FlowLac® 90	73.44 ± 2.96	0.54 ± 0.045



MATERIALS AND METHODS

GranuPack

- A steel cylindrical cell (D=26 mm, L=100 mm) is filled with powder, following a strict initialization protocol.
- The measurement cell performs free falls or "taps" to densify the granular medium.
- A distance sensor measure the height of the granular pile after each tap.
- The Bulk Density as a function of the number of tap is obtained.

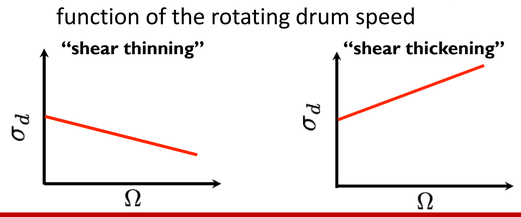


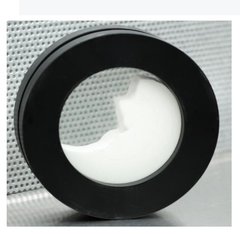
Evaluation of:

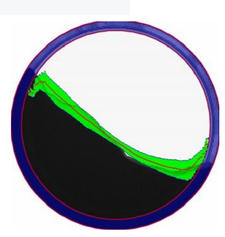
- Initial bulk density (ρ_0)
- Final bulk density (ρ_{500})
- Hausner ratio ($Hr = \rho_{500}/\rho_0$)
- Packing dynamic (α and $n_{1/2}$)

GranuDrum

- A horizontal cylinder with vertical glass side walls is half filled with the powder.
- The camera inside the equipment will measure the temporal fluctuation of interface and translate that to a cohesive index that can be used to assess the **flowability** of a given powder.
- Rheological behaviours can be evidenced with the Dynamic Cohesive Index **(DCI)** as a function of the rotating drum speed







RESULTS

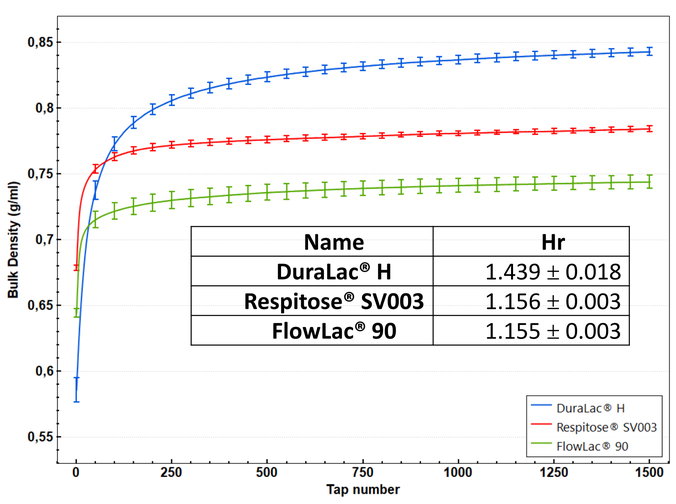
Aerosolization performance

Name	100 L/min	60 L/min	28 L/min
DuraLac® H FPM (mg)	0.80 ± 0.10	0.72 ± 0.01	0.62 ± 0.01
Respitose® SV003 FPM (mg)	0.74 ± 0.02	0.60 ± 0.04	0.38 ± 0.01
FlowLac® 90 FPM (mg)	0.20 ± 0.06	0.13 ± 0.02	0.01 ± 0.00

Data obtained with a Cyclohaler®, a capsule-based inhaler, discharged into a NGI [2]. About 40ml of powder was used for each discharge.

FPM: DuraLac® > Respitose® > FlowLac®

GranuPack analysis



Name	Hr
DuraLac® H	1.439 ± 0.018
Respitose® SV003	1.156 ± 0.003
FlowLac® 90	1.155 ± 0.003

- The Duralac® blend had the lowest initial density ρ(0), followed by the Flowlac® and then Respitose® ones.
- On the contrary, one can see that the Duralac® mixture has the highest tapped density ρ(1500), probably coming from the broader size distribution of the Duralac® [2], for which smallest particles can fill the voids between larger particles.

Hr: DuraLac® > Respitose® ≈ FlowLac®

- **Hr not enough to correlate with FPM.**

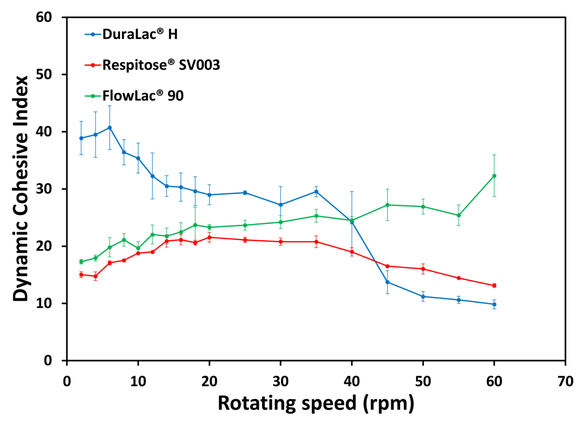
- Due to different rheological behaviours, the classification in term of cohesion is different considering low or high rotating speeds.
- The Aeration index versus the rotating speed increases for the DuraLac® blend, which could explain its shear-thinning behaviour. Air incorporated in the DuraLac® blend due to mechanical agitation could decrease the contacts and the interactions between particles and decrease the cohesion.
- Respitose® blend has an intermediate ability to be aerated, while the FlowLac® blend presents the worst propensity to be aerated, particularly at higher speeds, where the aeration ratio is gently decreasing with the rotation speed.

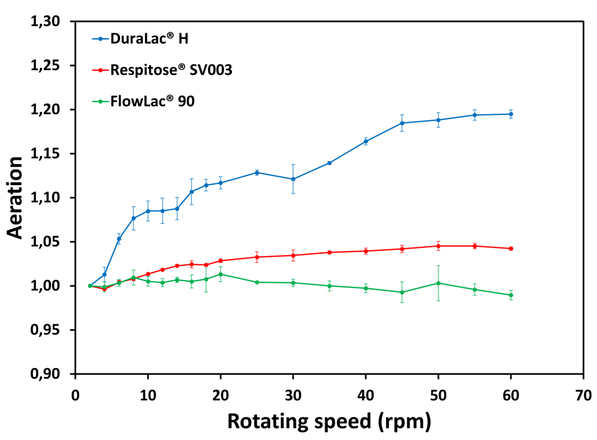
DCI (2 rpm): DuraLac® > FlowLac® > Respitose®

DCI (60 rpm): FlowLac® > Respitose® > Duralac®

- **High rotation speed corresponds to shear state undergone by DPI during aerosolization.**
- **DCI is well correlated with FPM at high rotation speeds and therefore in high shear rate conditions.**

GranuDrum analysis





CONCLUSIONS AND PERSPECTIVES

Three powders composed of a mixture of SS with different lactose grades were analyzed in this work. From these results the main conclusions can be drawn:

- The GranuDrum has evidenced **rheological behaviours**, drastically changing the classification proposed by quasi-static measurements.
- **Duralac®** blend exhibits **shear-thinning** behaviour.
- **Flowlac®** blend exhibits **shear-thickening** behaviour.
- **Duralac®** blend is found to be **the less cohesive** powder while **Flowlac®** blend is found to be the **most cohesive** powder **at high rotation speed**. Respitose® has an intermediate cohesiveness.
- DCI is well correlate to FPM for high rotation speeds.

REFERENCES

[1] Benque B and Khinast J G: *Understanding the motion of hard-shell capsules in dry powder inhalers*, Int J Pharm 2019; 567: p118481.

[2] Pinto J T, Cachola I, Pinto J F and Paudel A: *Understanding carrier performance in low-dose dry powder inhalation: An in vitro–in silico approach*, Pharmaceutics 2021; 13: p297.

[3] Neveu A, Crowley M and McGorisk T: *Characterisation of lactose for DPI applications*, OndrugDelivery 2021; 119: pp. 46-50.