METERED DOSE INHALERS (MDIS) PARTICLE SIZE DISTRIBUTION

Context

Inhalers are used to treat various pulmonary diseases, such as asthma, chronic obstructive pathologies, and certain lung cancers. These products contain Active Pharmaceutical Ingredients (APIs) fixed on nano or micro-sized particles that are dispersed in a pressurized gas in liquid form. The effectiveness of these inhalers depends on the penetration depth of the API into the lungs, which is dependent on the particle size distribution (PSD). To obtain reliable results, the PSD of inhalers must be measured in pressurized media to be consistent with the final use (spray, fine mist). However, there is currently no non-invasive method to directly provide this measurement.
In this study, we present a new non-invasive, and fast method for PSD characterization of pharmaceutical pressurized inhalers using TURBISCAN.

Pharmaceutical inhalers

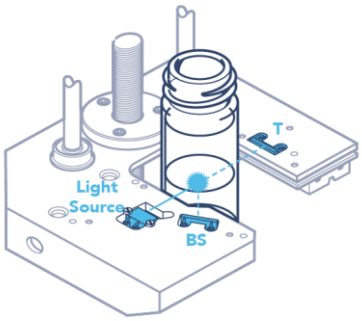
Also known as metered-dose inhalers (MDIs), pressurized pharmaceutical inhalers are designed to deliver a precise amount of medication in the form of a fine mist or spray when the user presses down on the canister.

Composed of active pharmaceutical ingredients (APIs) that are dispersed in a liquid form under pressure, the particle size is a critical factor in determining the efficiency and effectiveness of the inhaler. Particle size affects penetration depth into the lungs, and therefore the API delivered dose. On top of that, sedimentation and creaming can occur over storage impacting API particle size.

To ensure that pressurized inhalers are delivering the proper dose, several techniques can be used to measure PSD. However, accurate dose delivery is highly linked to the way the inhaler is used. TURBSICAN, based on SMLS technology, is a unique technique providing the ability to measure APIs PSD directly in the canister.

TURBISCAN: How it works

TURBISCAN technology is based on Static Multiple Light Scattering (SMLS) and consists of sending a light source on a sample to acquire a backscattered and transmitted signal all over the height of a sample in its native state. By repeating this measurement over time at an adapted frequency, the instrument enables monitoring the physical stability of a sample without any dilution.



$$BS = f\ (\varphi,\ d,\ n_p,\ n_f)$$

Figure 1. TURBISCAN measurement head

The signal is directly linked to the particle's concentration (φ) and size (d) according to the Mie Theory, with (n_f) and (n_p) being fixed parameters.

Measurements are performed without any dilution & on native samples up to **95v/v%** and **from 10nm up to 1mm.**

PSD with TURBISCAN is based on particle migration and automatic detection of the migration fronts with smart data analysis based on Stokes law and Mie theory[1].

From the T and BS profiles obtained of migrating particles (settling, creaming), the PSD can be computed (Figure 2).

The profiles can be converted into a particle velocity distribution and a size distribution of the sample normalized according to the intensity, the volume, or the number of particles as follows:

- Velocity distribution: no parameter is required and can be directly converted from T and BS profiles.
- PSD based on intensity: density and viscosity values of the continuous liquid, density, and the concentration of the dispersed phase.
- For PSD normalized according to the particle number or volume: in addition to previous parameters, refractive indexes of both continuous and dispersed phases are also required.

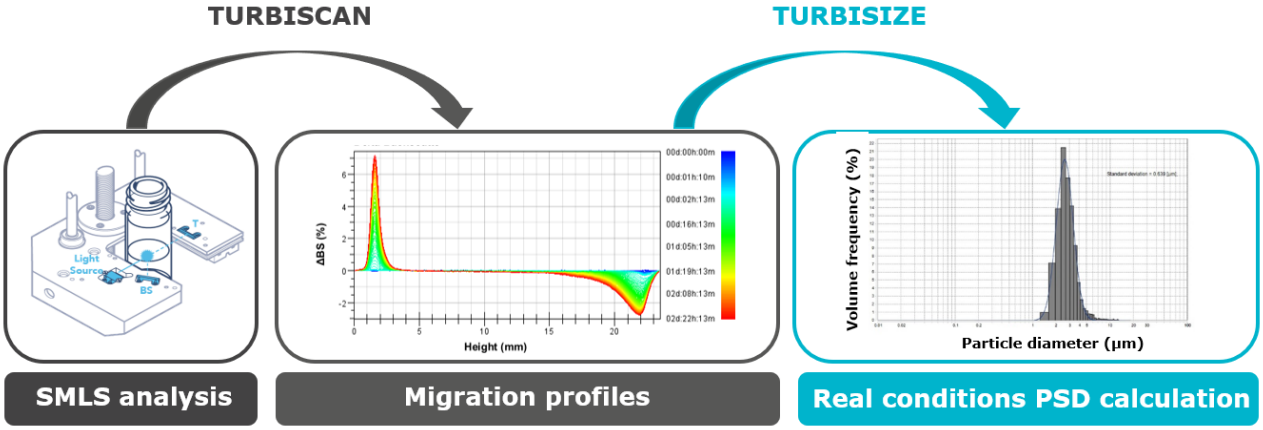


Figure 2. From TURBISCAN data to PSD with Turbisize

[1] *Matthias P.L. Sentis, Guillaume Lemahieu, Elizabeth Hemsley, Matthieu Bouzaid, Giovanni Brambilla, Size distribution of migrating particles and droplets under gravity in concentrated dispersions measured with static multiple light scattering, Journal of Colloid and Interface Science, Volume 653, Part B, 2024, Pages 1358-1368, ISSN 0021-9797, https://doi.org/10.1016/j.jcis.2023.09.163.*

The Study

The samples

Four salbutamol sulfate API-based inhaler samples with different particle sizes were selected (S1, S2, S3, and S4).

Figure 3. Photo of the tested pressurized inhalers

In each sample, the same API particle system (dispersed phase) is used in combination with two different low-GWP (Global Warming Potential) pressurized propellants (continuous phase). The API particle system density (ρ) is about 1.3 $g.mL^{-1}$ with a refractive index of 1.566.

The differences between samples are related to the manufacturing process regarding the milling grade of API particles with the same process used for:

- S1 and S2 (Process 1)
- S3 and S4 (Process 2)

The impact of the propellants on the milling grade of API is investigated with the same propellants used for :

- S1 and S3 (Propellants A: density (ρ) about 1.226, with a viscosity (η) of 0.2 cP and refractive index about 1.223.)
- S2 and S4 (Propellant B: density (ρ) about 1.0.912, with a viscosity (η) of 0.16 cP and refractive index about 1.243)

To summarize:

Milling Process 1		Milling Process 2	
S1	S2	S3	S4
Propellant A	Propellant B	Propellant A	Propellant B

Table 1. The 4 tested samples' specifications

The Results

First, each pressurized inhaler sample is directly pre-homogenized using a vortex stirring device at 1000rpm for 2 minutes without any additional preparation.

The measurement is performed with the TURBISCAN over 1 hour at 25°C.

The transmission (T%) and backscattering (BS %) variations are represented as a function of sample height (in mm) over time. The bottom of the sample is represented on the left part of the graphic and the top of the sample is on the right part. The color gradient on the time scale corresponds to each scan time lapse with the first scan in blue and the last scan in red. In the following graph, the settling profile recorded for S1 is displayed.

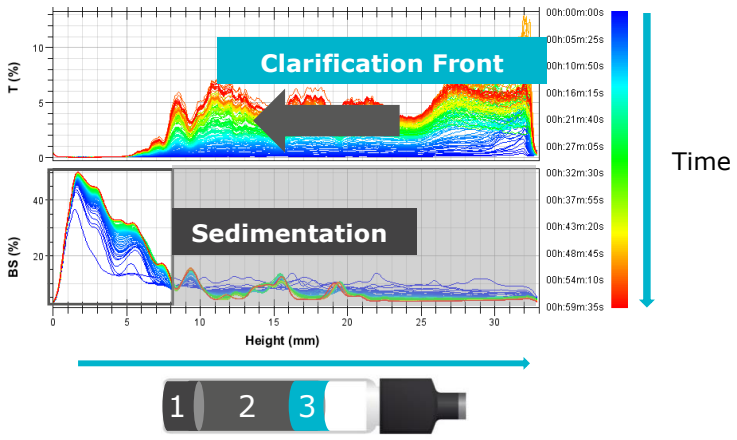


Figure 4. Transmission and Backscattering profiles for samples S1 (a)

Based on the graph, the destabilizations identified are:

- At the bottom of the sample (1) – BACKSCATTERING- left side of the graph- the Backscattering signal increases with time, which means more and more scatterers are present in this area. The API particles sediment and locally change the suspension's concentration. A SEDIMENT is formed over time.

- At the top of the sample (3) - right side of the graph – TRANSMISSION- the transmission signal increases in intensity and height, fewer scatterers are present at the top and the suspension becomes less concentrated. A CLARIFICATION layer is formed over time.

By processing these profiles for the 4 samples using TurbiSize software, the volume-based PSD of each pressurized inhaler is obtained.

The following Figure 5 presents the PSD for the four tested samples.

Based on the results :

- For the same Process, samples with Propellant B present a lower size distribution and polydispersity.

- For the same Propellant, samples manufactured with Process 1 present a lower size distribution and polydispersity.

Therefore, the results obtained identify the process used for samples S1 and S2 as the more efficient to produce reduced API particle sizes. In addition, the propellant used for manufacturing sample S2 (Propellant B) seems to be the most suitable as it allows to obtain a reduced bulk PSD for API particles in pressurized inhalers. This lower PSD is an indicator of improved API therapeutic administration, as the particles can penetrate the lungs more deeply and efficiently.

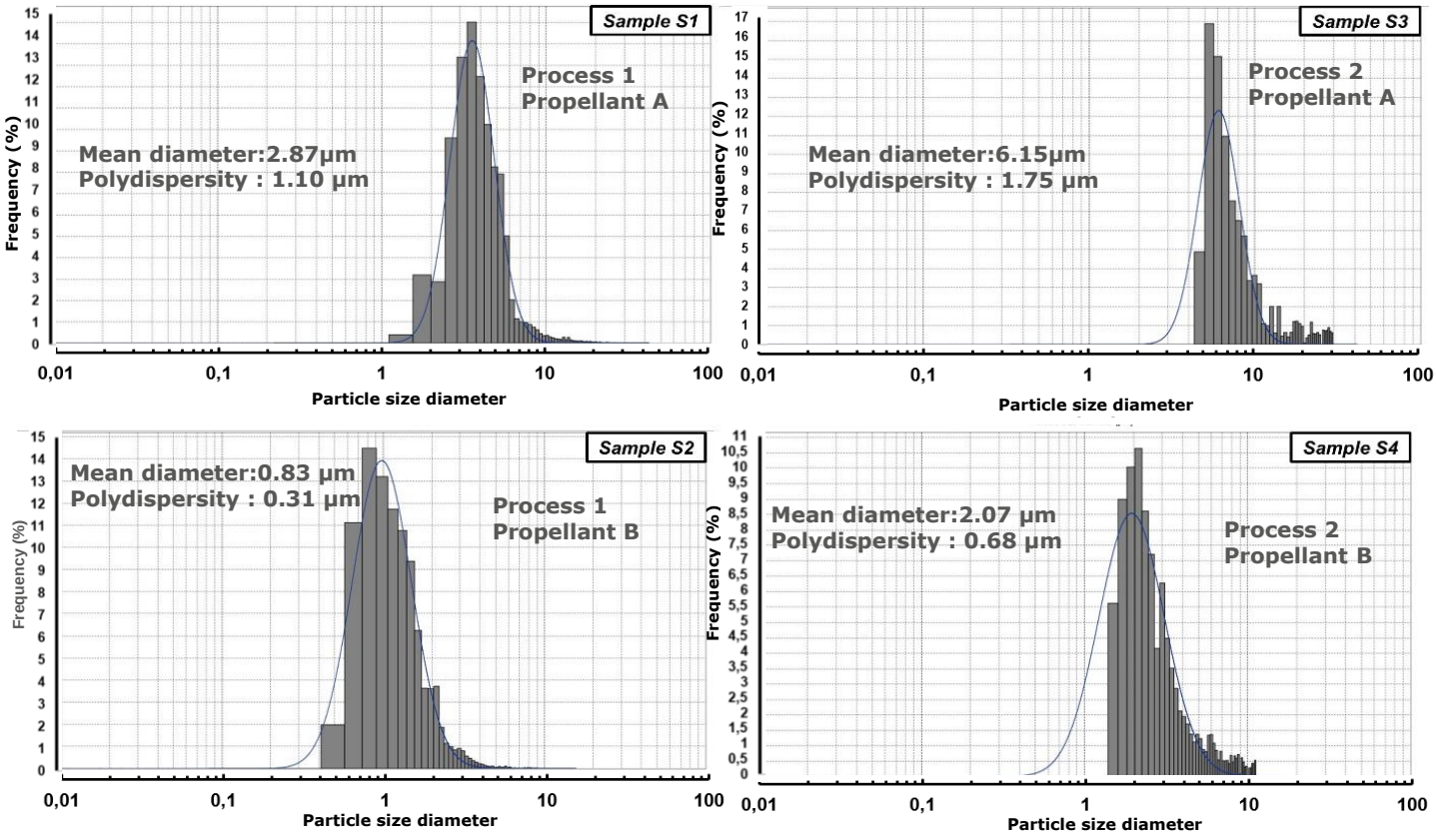


Figure 5. Intensity-based PSD profiles using Turbisize for the 4 pressurized inhalers

Conclusion

To quantify and compare the PSD of pharmaceutical pressurized inhalers, the TURBISCAN was used to measure in real storage conditions. SMLS technology suits perfectly the need in the pressurized inhalers market as it's THE unique technology able to evaluate the PSD directly inside pressurized inhalers in a non-invasive way. By understanding APIs settling and PSD, the proper dose delivery can be controlled. In addition, other challenges can be met like new API molecule development, and substitution of classical fluoro-gazes used, which are known to deplete the ozone layer, by low Global Warming Potential (GWP) propellant.

This Application note is the result of a collaborative study with **NANOPHARM**, globally recognized as one of the major actor in the design and development services for orally inhaled and nasal drug products, such as materials characterization, formulations, and inhaled biopharmaceuticals development

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