Direct particle size distribution measurement of an active ingredient suspended in pressurised metered dose inhalers and parameters which influence migration rate

Cristina Rey Blanes[1], Luca Serratore[1], Katie Reichwald[1], William J Ganley[1], Jose Ferrao[2], Marie-Laure Vicenty[2], Guillaume Lemahieu[3], Matthias Sentis[3], Giovanni Brambilla[3], Robert Price[1], Jagdeep Shur[1] and Irene Rossi[1]

[1]Nanopharm, An Aptar Pharma Company, Grange Road, Cwmbran, NP44 3WY, United Kingdom

[2]Aptar Pharma, Route des Falaises, Le Vaudreuil, 27100, France

[3]Formulaction, 3-5 Rue Paule Raymondis, Toulouse, 31200, France

Key Message

In the re-formulation of suspension pMDIs in low-GWP propellants, the investigation of the influence of the active ingredient's PSD on sedimentation is fundamental. In this study, we directly measured the particle size of a suspended API in pMDIs and we correlated this average diameter, propellant density and raw API PSD with migration rate.

Introduction

Since the adoption of the Kyoto Protocol in 1997, the European F-Gas regulation have made further amendments which aims to reduce the use of F-gases by 98% by 2050 [1]. HFA propellants have a higher Global Warming Potential (GWP) and therefore, will impact climate change.

The particle size distribution (PSD) of the active ingredient suspended in the propellant has an important role in determining the respirable fraction and the stability and reproducibility of performance of pMDI [2]. For a successful transition to low-GWP propellants (HFA 152a and HFO 1234ze), it is important to understand what is their influence on suspension stability, sedimentation rate and particle size of the API suspended.

Nowadays, there is no effective method for measurement of the PSD of the suspended active in the final pMDI. In this study, we have explored a new feature of SMLS technique, which allows for the measurement of the migration rate and PSD of the API particles suspended in the propellant by analysing directly the pressurised formulation in its native state.

Experimental Methods

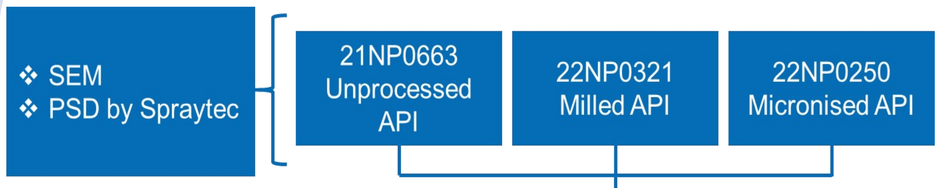

Table 1. Propellant Properties

Propellant	Density (g/mL)	Viscosity at 25°C (cP)
HFA 134a	1.23	0.20
HFA 227ea	1.41	0.21
HFA 152a	0.91	0.16
HFO 1234ze	1.19	0.199

Four different propellants were studied (Table 1). Migration rate and PSD were measured directly in the pressurised inhaler with a static multiple light scattering (SMLS) based device (Turbiscan LAB, Formulaction, France) [3,4].

Figure 1 summarises the PSD assessment using SMLS. Data obtained were finally input in a full factorial model employing JMP SAS (USA) to assess the influence of each parameter on the migration rate.

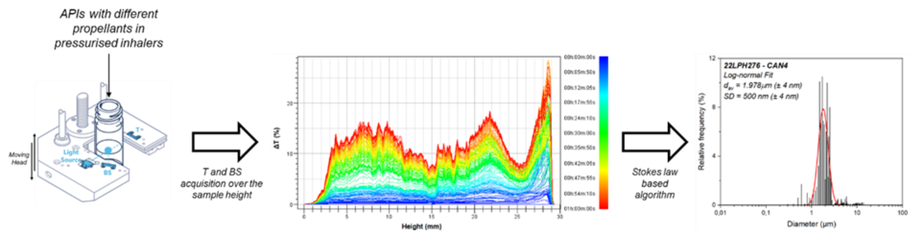

Figure 1. Summary of PSD analysis by Turbiscan LAB

Results and Discussion

The three salbutamol sulphate APIs were characterised for particle size distribution upon wet dispersion (Table 2). Generally, they presented different particle size and span (width of the distribution). The micronised API (22NP0250) showed the lowest PSD, the most suitable for inhalation, whereas the unprocessed (21NP0663) and milled API (22NP0321) showed a broader PSD (21NP0663 > 22NP0321) and a much higher volume diameter Dv50 (16.68 µm for 21NP0663 > 12.77 µm for 22NP0321).

Differences in particle size were also visually confirmed by SEM (Figure 2) with 21NP0663 presenting the largest crystals and the least uniform PSD (multimodal) compared to the other two APIs screened.

Table 2. PSD of raw APIs (n=3) ± Standard Deviation

PSD wet cell Spraytec				
Batch	Dv10 (µm)	Dv50 (µm)	Dv90 (µm)	Span
21NP0663	3.83 ± 0.16	16.68 ± 0.10	61.81 ± 6.94	3.48
22NP0321	3.29 ± 0.16	12.77 ± 0.37	38.02 ± 3.21	2.72
22NP0250	0.89 ± 0.03	1.87 ± 0.07	3.93 ± 0.21	1.62

Figure 2. SEM pictures of the three APIs employed for the study (all 5000x magnification)

Turbiscan has been used to measure the migration rate and the resulting PSD of the API suspended in the four different propellants (Figure 3 and Figure 4). The average particle size diameter (Dav) was in line with the PSD measured by Spraytec for all propellants. In addition, API suspended in HFA 152a reported a quicker sedimentation when compared to the rest of propellants. However, migration rate appeared to be comparable between the three API employed with no direct correlation between migration rate and PSD of the API.

All parameters and their combination had a statistically significant effect on migration rate with the average particle size diameter taken alone having the least effect (lowest Log-Worth, namely -log10(P value), and higher P value) (Table 3).

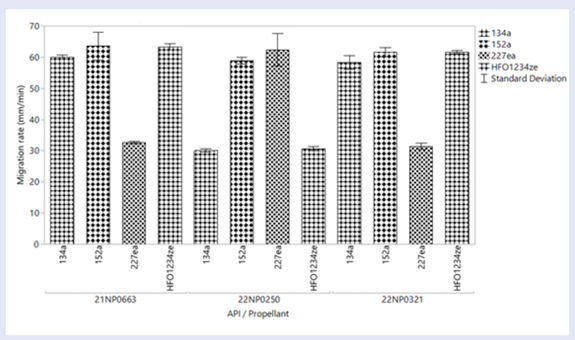

Figure 3. Migration rate obtained by Turbiscan LAB (n=3, bars represent standard deviation)

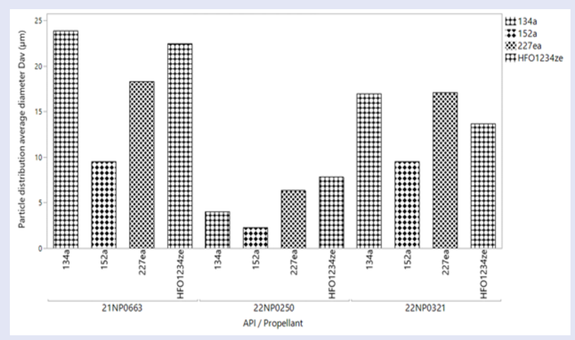

Figure 4. Average Particle Size Diameter (Dav) of the PSD obtained by Turbiscan LAB (n=1)

Table 3. Full factorial fit model results

Source	LogWorth	PValue
API PSD*Propellant Density (g/mL)*Dav by Turbiscan	23.900	0.00000
API PSD*Propellant Density (g/mL)	23.601	0.00000
Propellant Density (g/mL)	16.712	0.00000
API PSD	13.423	0.00000
Propellant Density (g/mL)*Dav by Turbiscan	9.714	0.00000
API PSD*Dav by Turbiscan	3.635	0.00023
Dav by Turbiscan	1.526	0.02976

Conclusion

A new method for the measurement of the migration rate and PSD of an API suspended in traditional and low-GWP propellants was investigated.

A comparison of the behaviour of the SS batches with different PSD in new and traditional propellants was carried out and the influence of PSD on the migration rate and stability of MDI suspensions was reported.

This study showed that it is possible to directly measure the particle size of a suspended API in pMDIs employing Turbiscan LAB.

Particularly, migration rate is known to influence aerodynamic particle size distribution and drug delivered [3]. Therefore, being able to contemporary measure PSD and migration rate of API suspended in MDI can facilitate the re-formulation of current pMDIs in low-GWP propellants and the development of bioequivalent products.

References

1. EU legislation to control F-gases. Available from: https://ec.europa.eu/clima/eu-action/fluorinated-greenhouse-gases/eu-legislation-control-f-gases_en. Accessed July 3 2022.
2. Sheth P, Stein W S, Myrdal B P, Factors influencing aerodynamic particle size distribution of suspension pressurized metered dose inhalers, AAPS J 2015; 16(1): pp 192-201.
3. Myrdal P B, Sheth P, Stein S W, Advances in Metered Dose Inhaler Technology: Formulation Development, AAPS J 2014; 15(2): pp 434-455.
4. Luo M, Qi X, Ren T, Huang Y, Keller A A, Wang H, Li F, Heteroaggregation of CeO2 and TiO2 engineered nanoparticles in the aqueous phase: Application of turbiscan stability index and fluorescence excitation-emission matrix (EEM) spectra, Colloids and Surfaces A: Physicochemical and Engineering Aspects 2017; 533: pp 9-19.