Assessment of Suspension Characteristics of Budesonide Micronized by Traditional Jet-Milling and by Sonocrystallization in High and Low Global Warming Propellants

James Murray,[1] Sally Stanford,[1] Anna Vivani,[2] Andrea Silvestri,[2] Sheryl Johnson,[1] Marco Laackmann[3] and Irene Rossi[3]

[1]Orbia Fluor & Energy Materials (Koura), Chester, UK

[2]Sterling, Corciano, 06073, PG, Italy

3Harro Höfliger, Allmersbach im Tal, 71573, Germany

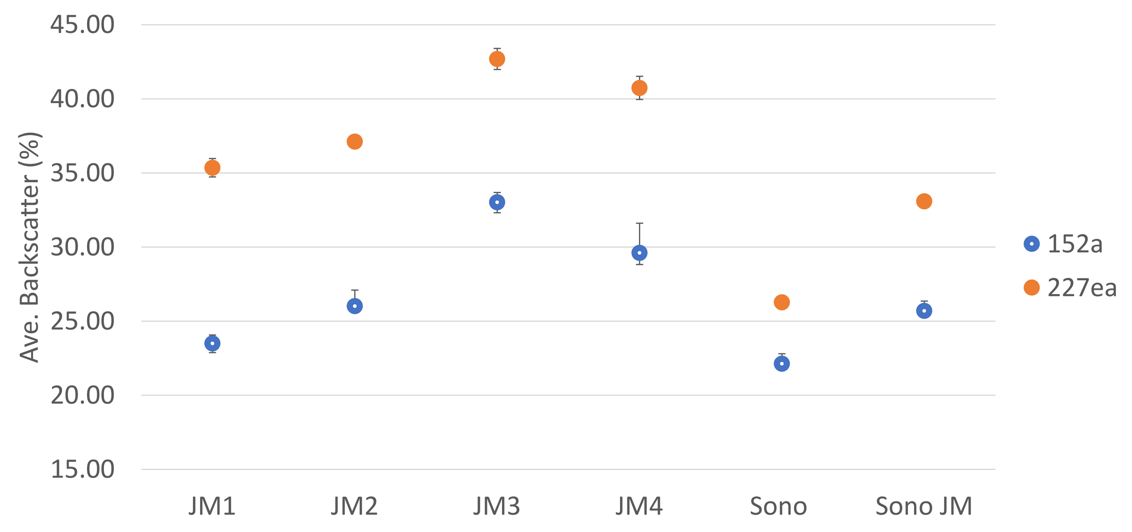
Introduction & Methods

Using 1,1-difluoroethane (HFA152a) in metered dose inhaler (MDI) formulations reduces the carbon footprint by > 90% compared to HFA-134a. However, 152a differs physicochemically from high global warming potential (HGWP) propellants. Its lower density (0.91 g/ mL vs. 1.23 g/mL for 134a and 1.41 g/mL for 227ea) may affect migration rate. Likewise, properties of the suspended micronized drug influence suspension homogeneity, flocculation and migration.

Traditional jet-milling (JM), though an effective method of micronization, is energy-intensive and can alter particle structure. Sonocrystallization (Sono), a power ultrasound-assisted technology, improves particle attributes for better lung delivery. This study examines how micronized budesonide's physical properties, shaped by micronization processes, affect its suspendability in HGWP and LGWP propellants.

Jet-milling	Sonocrystallization
<u>Principle Control Parameters</u> -Grinding & feeding energy -Feeding rate -Mill size & geometry	<u>Principle Control Parameters</u> -Ultrasonic power -System temperature -Injector diameter
<u>Pros</u> -Very narrow size distribution -Continuous process	<u>Pros</u> -Tailored & consistent morphology -High degree of crystallinity
<u>Cons</u> -Can cause defects in crystal lattice (amorphous regions) that requires conditioning. -Yield negatively affected by coating/crusts on long runs	<u>Cons</u> -Solvent/Anti-solvent compatibility -Usually long drying step needed

Results: Dispersions of Budesonide Suspension



Average dispersion is shown above and represents the average Backscatter obtained in the middle of formulation at T=0. The trend generally follows the particle size distribution shown in Table 1, with the smaller particle size producing more disperse formulations.

However, for the sonocyrstallised material in 152a it is interesting to see that a similar dispersion is seen to JM1 which has approximately half the particle size distribution of the sono-crystalised material, indicating that for this propellant a favourable interaction between the 'plate like' morphology is achieved.

Analysis: Budesonide Characterisation

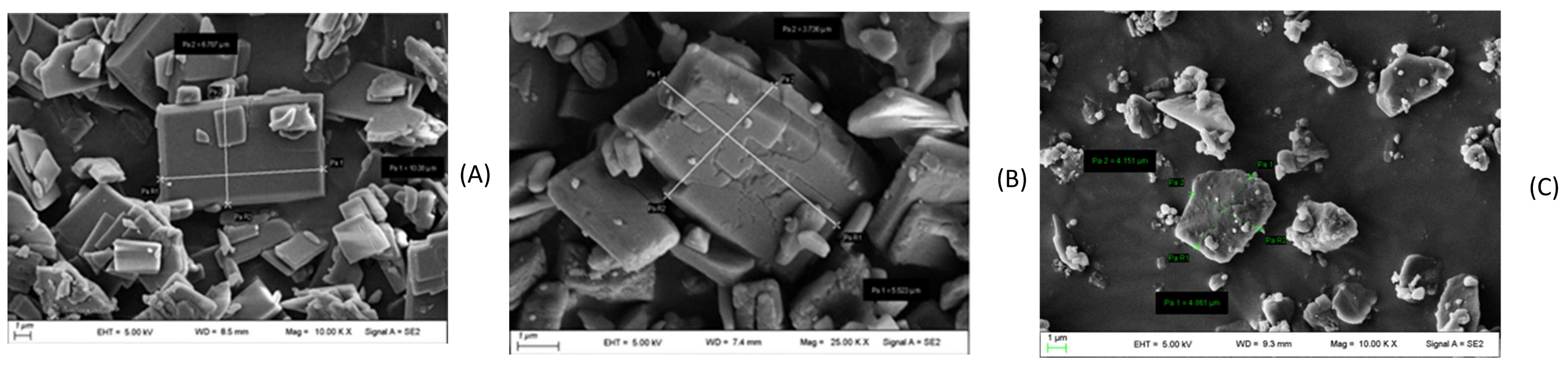


Figure 1: SEM images of Budesonide from sonocrystallisation (A), From sonocrystallisation followed by jet-milling (B) and jet milling, (C)

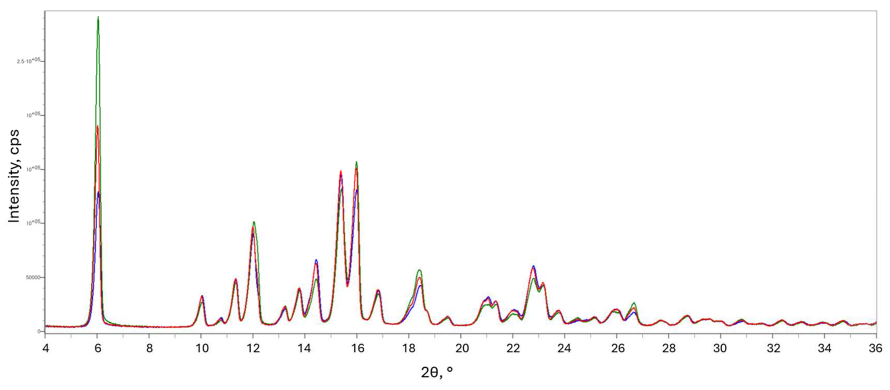
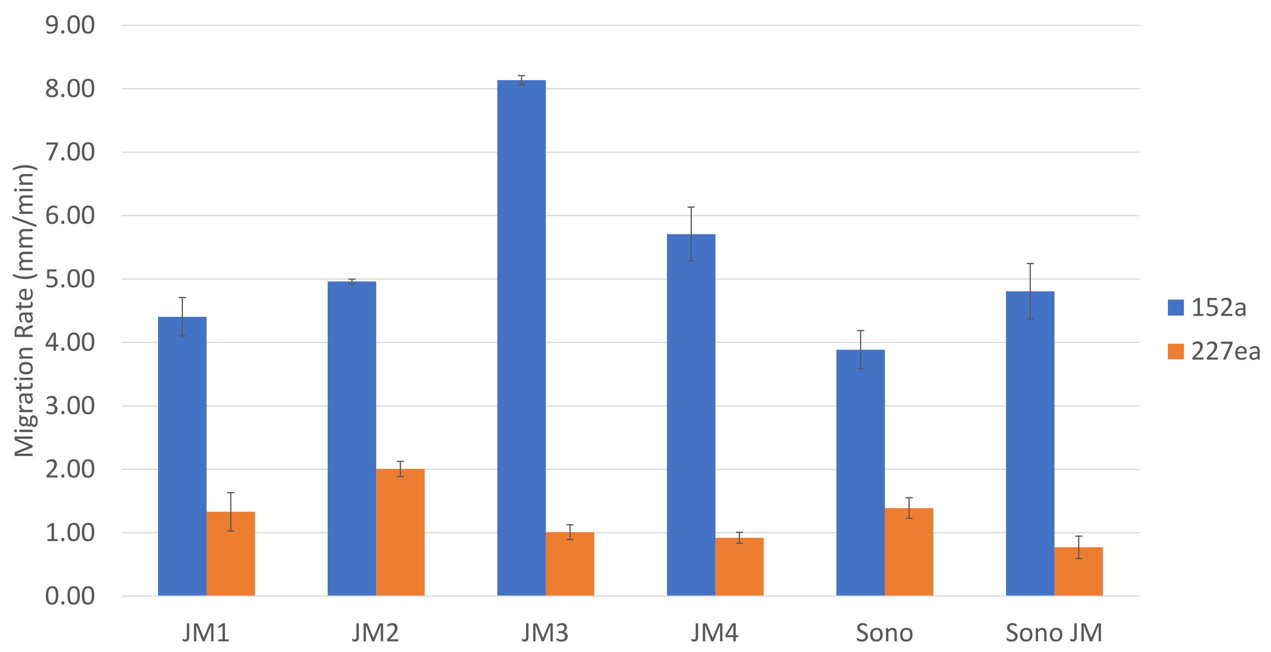


Figure 2: XRD results for sonocrystallised material (green), Jet-milled (blue) and sonocrystallised followed by jet-milling (red).

Budesonide Batch	D10 (µm)	D50 (µm)	D90 (µm)	Span
Sono	1.8	4.5	8.6	1.5
Sono JM	1.2	2.5	4.5	1.3
JM1	0.9	2.1	4.5	1.7
JM2	0.9	2.1	4.5	1.7
JM3	0.7	1.3	2.8	1.6
JM4	0.7	1.6	3.1	1.5

Table 1: PSD of Budesonide manufactured by jet-milled or sonocrystallisation

Results: Migration of Budesonide Suspension



The migration rates of the two propellants are shown above. The rate is calculated by assessing either the creaming or sedimentation peak thickness over time.

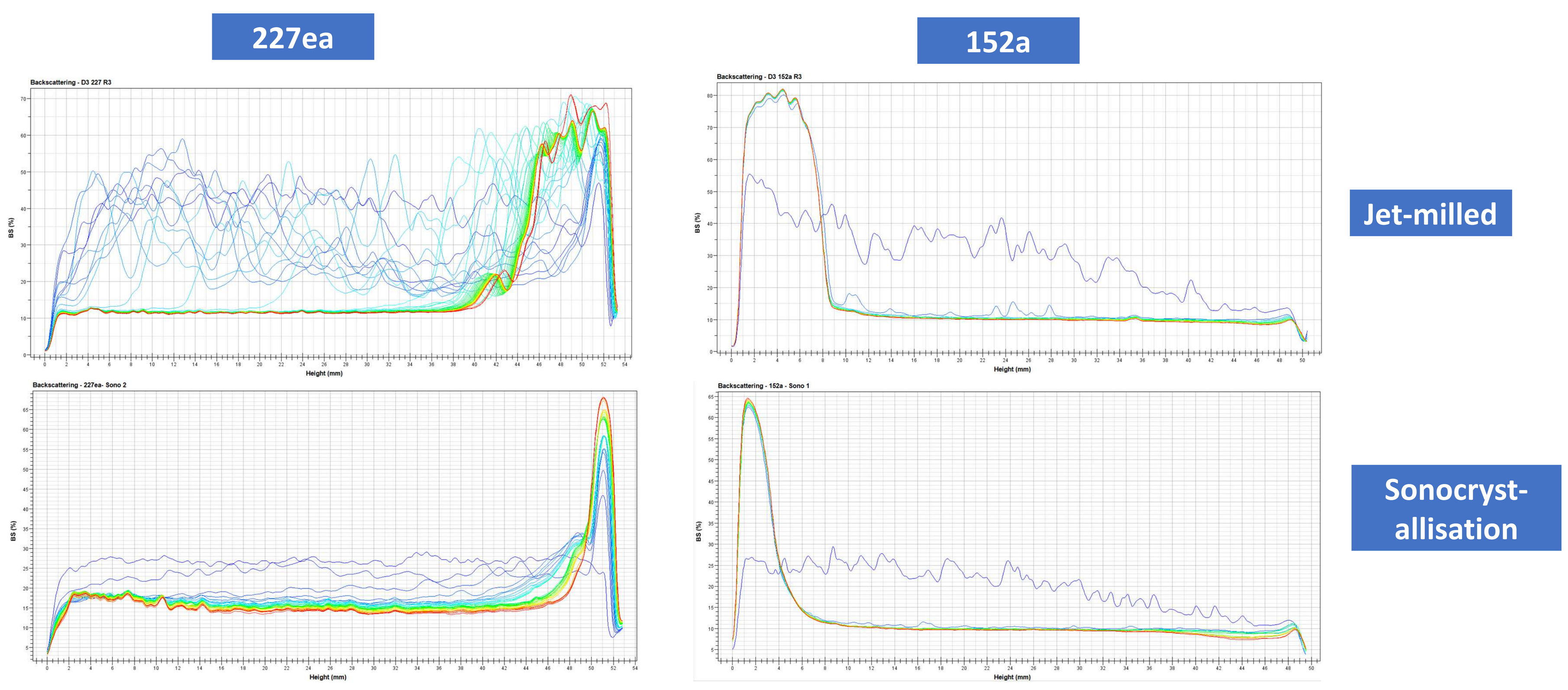
The sonocrystallised material had a marked effect on reducing the migration rate for the 152a formulations when compared to JM3 & JM4 and had a minor effect on the JM1 & JM2 formulations. There were limited differences between the migration rates of the Budesonide batches in 227ea

Results: Budesonide Characterisation

Sonocrystallisation technique obtains Budesonide particles with a respirable size and narrow distribution (Table 1). Interestingly, sonocrystallised particles showed a well-defined plate-like morphology, clear edges and smooth surfaces (Figure 1, A). Reduced PSD was obtained by low-energetic jet-milling of the obtained Budesonide (Table 1, Sono JM). Notably, plate-like morphology of the input material was retained after jet-milling (Figure 1, B). However, a few crystal fragments were also observed, which is typical of micronised material.

In contrast, clearly different morphology was observed for Budesonide products which were obtained from classic precipitation and subsequent jet-milling treatment, which show irregular particles with no well-defined shape and some crystal fragments (Figure 1, C). Comparable results in terms of polymorphism and structural properties were obtained for all samples from XRPD measurements (Figure 2).

Results: Qualitative Review of Budesonide Suspensions



Qualitative comparison and benefits of sonocrystallised material

- Gaussian peaks ✓
- Less variation in particle size ✓
- Smooth migration ✓
- More homogeneous ✓

Summary & Conclusions

•The Sonocrystallisation process produced micronised Budesonide with a D50 <5 µm.

•The process produced consistent plate-like morphology. Even when further processed by jet-milling to reduce particle size.

•Our investigations demonstrated that comparable dispersion was achieved between sonocrystallised and jet-milled material, even in the case of a higher particle size distribution.

•The sonocrystallised material produced the most favourable migration rate in the LGWP propellant.

•The sonocrystallised material resulted in a Budesonide suspensions with vastly improved homogeneity.

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Harro Höfliger