High pressure homogenization as an alternative methodology to micronization for obtaining effective inhalation particles

Case studies for the industrial manufacture of inhalation grades of fluticasone propionate and mometasone furoate monohydrate

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Photo courtesy of Hovione.

Background

One of the key factors affecting delivery of drugs to the lungs is particle size. This is relevant for both dry powder inhaler (DPI) and suspension pressurized metered dose inhaler (pMDI) formulations. Depending upon the specific airway target site, the particle size can vary slightly but generally, an aerodynamic particle size distribution (PSD) of 1-6 µm is required for successful inhalation therapy.[1]

Product specific optimization of particle size distribution is important for several reasons:

- to reduce dose variability into the lung
- to maximize the proportion of drug in the finished product formulation that reaches the target airway site; this in turn minimizes the active content in the formulation required for an efficacious response and reduces the likelihood of potential side effects
- in the area of generic product development, to be able to demonstrate in vitro and subsequently in vivo equivalence to a reference product

The DPI and suspension pMDI formulations therefore require the incorporation of the active pharmaceutical ingredient (API) in a well defined and controlled particle size distribution. Historically, the production of such particles has been performed using the processes of batch crystallization followed by size reduction using air jet milling (micronization), a technology available for more than 100 years. Micronization has been used for the development of inhalation products since the 1960s, with significant challenges commonly referred to in the literature and observed by Hovione in its 30-plus years utilizing the technology.

- It is a high energy size reduction process that breaks down active substance crystals, impacting surface energy and crystal form. The output material often contains significant amorphous content, which can influence the stability of the finished product formulation.[2]
- In order to produce the desired particle size, jet milling frequently requires a number of repeat runs. It is therefore an inefficient process that creates the potential for metal contamination from the extended high energy contact with the micronizer metal components. In addition, the amorphous content increases with each repeat run.

High Pressure Homogenization

In the quest to find alternatives to air jet milling for the production of powders for inhalation, several top-down and bottom-up technologies have been widely reported in specialized literature.[3,4] One of these alternatives is the top-down technology high pressure homogenization (HPH). Hovione has developed a novel and proprietary[5] technology using HPH that provides an alternative to air jet milling.

The process consists of suspending the product of interest in a suitable anti-solvent. The slurry is then subjected to high pressures, passing through a small orifice or channel (less than 300 μm). The velocity of the suspension increases as does the dynamic pressure of the fluid. At the same time, the static pressure of the fluid decreases and gas bubbles form. After this, the channel widens causing the gas bubbles to implode (cavitation), thus generating high energy shock waves responsible for particle breakage. Some equipment is also designed to promote inter-particle collision and high fluid shear forces, thus increasing the efficiency of the process.

In general terms, the advantages of HPH, beneficial to particle reduced APIs are the production of powders with tunable PSDs and a high level of reproducibility as demonstrated in Figure 1 (2% stdev against a typical 16% stdev in micronization).

In specific cases, like the ones of fluticasone propionate and mometasone furoate monohydrate presented in this article, HPH may be an enabling technology, to avoid the formation of amorphous domains or keep the polymorphic (e.g: monohydrate) form. This might be explained by the absorption of the excess energy in particle breakage by the anti-solvent, thus minimizing changes in the crystal lattice.

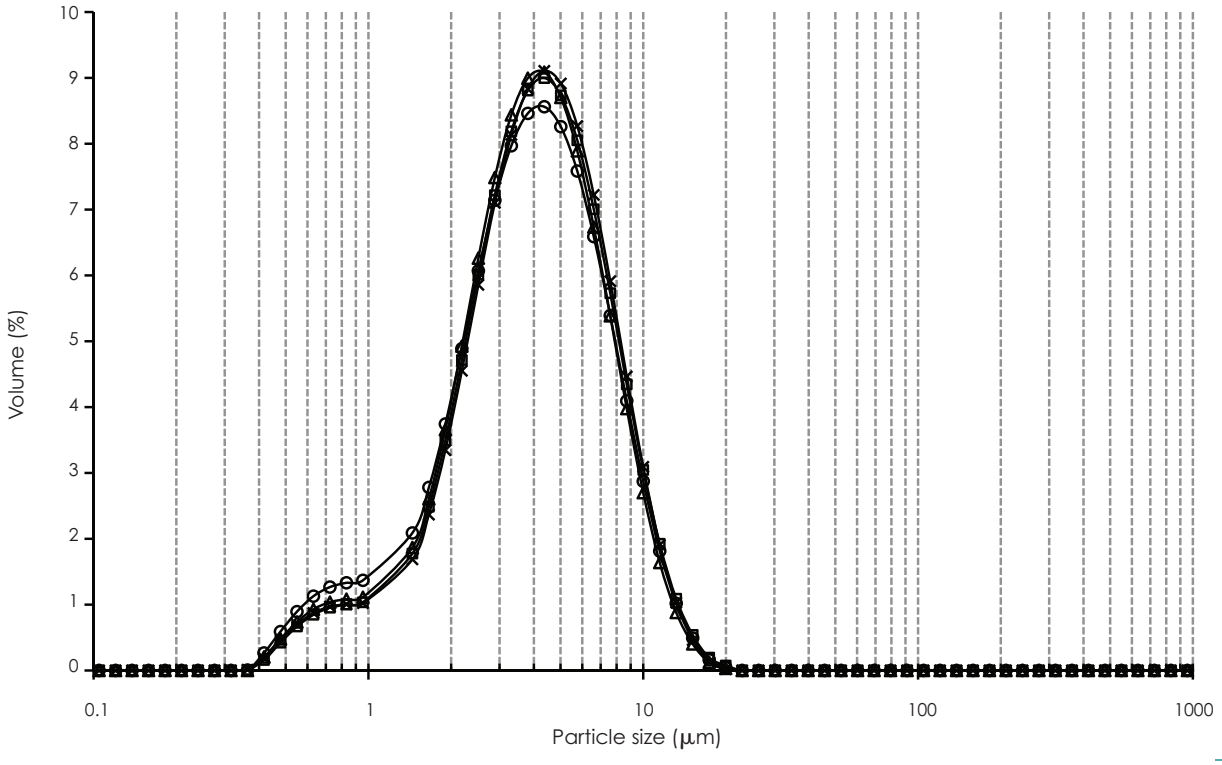
Case Studies

Fluticasone Propionate

Fluticasone propionate (FP) is a synthetic corticosteroid with anti-inflammatory activity, particularly

Figure 1

Particle size distribution of four batches produced by HPH and SD process.



useful for the treatment of respiratory disorders such as asthma, and is delivered by pMDIs and DPIs. FP crystalline solid Form I is characterized by the x-ray powder diffraction (XRPD) pattern presented in Figure 2a). The melting temperature of this form, as determined by differential scanning calorimetry (DSC), is approximately 287 ºC.

In addition to crystalline solid Form I, the disorder amorphous solid form can be easily obtained via spray drying. Figure 2b) shows that no diffraction peaks are observed in the corresponding XRPD pattern; only a halo centered at approximately 14 º 2θ is detected, which confirms the amorphous nature of the product. The corresponding DSC data acquired (data not shown) corroborates the XRPD pattern. In fact, a glass transition is detected at approximately 76 ºC and immediately followed by an exothermic transition at 96 ºC, which corresponds to crystallization of the supercooled liquid state. Melting occurs at the same temperature as Form I (287 ºC), which proves that this is the solid form crystallizing at 96 ºC.

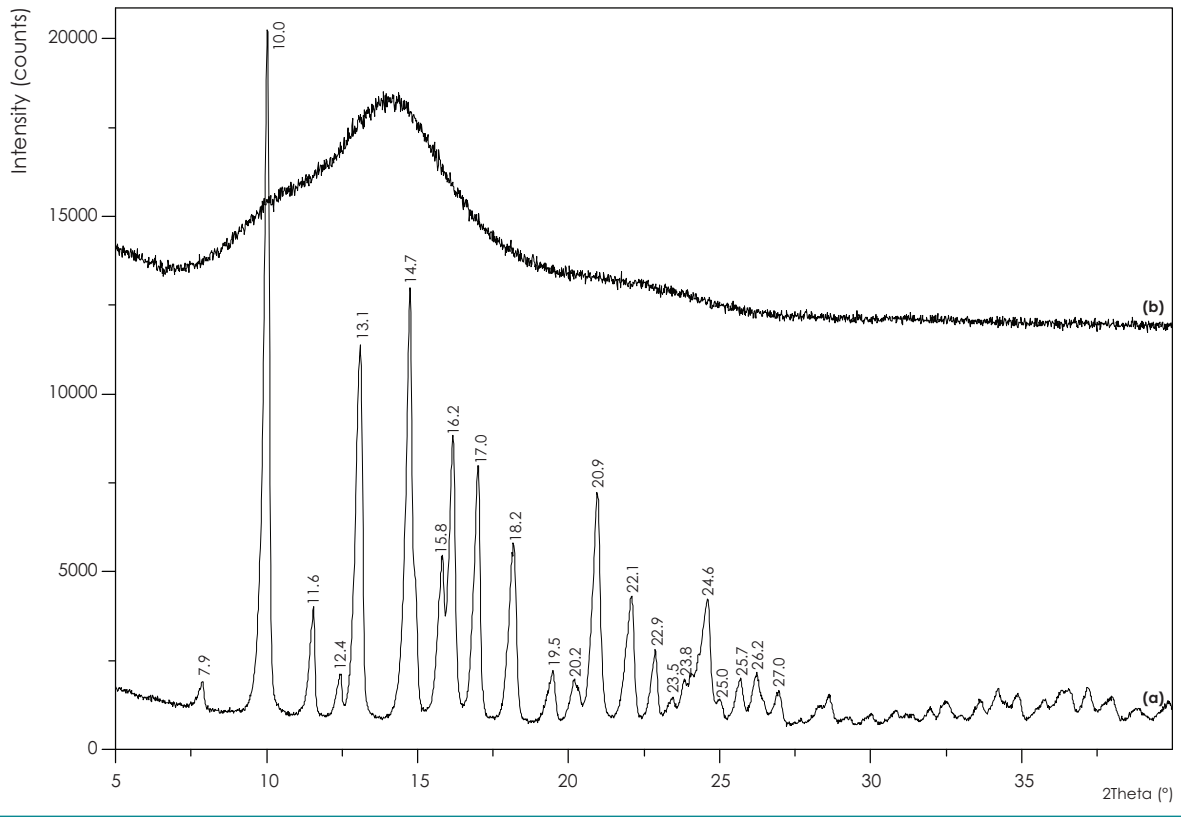
The relatively low T_g (76 ºC) and the fact that crystallization readily occurs after crossing the glass transition region, indicates that this metastable state, once formed, is easily converted to crystalline Form I.

The energy involved in micronization processes (e.g. air jet milling) can lead to the disruption of the crystalline structure with the consequent formation of amorphous domains. Figure 3 gives the evaluation by XRPD of the influence of air jet milling micronization on FP. Traces a) and d) correspond to the references non-micronized material (100% crystalline) and to the spray-dried solid powder (100% amorphous), respectively, while traces b) and c) are the XRPD patterns of FP after one and two micronization passes, respectively. With micronization, XRPD baseline curvature increases and peak intensity decreases, with the patterns getting closer to the XRPD trace of the amorphous form. This means that with micronization, the content of amorphous form is increasing. In fact, quantitative XRPD analysis indicates that, after the first pass, the content of amorphous form is already as high as 47% (w/w). Moreover, this amount increases to 75% (w/w) with the second run.

As described, high amounts of amorphous form of FP can be produced during air jet milling micronization, i.e., a solid phase transformation occurs during the micronization process. Due to the metastable nature of this form, this will have a strong impact on the stability of the material and its properties. This phenomenon is shown in Figure 4. The amount of

Figure 2

XRPD patterns of non-micronized FP Form 1 (a) and of amorphous FP (b).



amorphous material,*, for samples left at room conditions, was measured as a function of time. Simultaneously, water content and particle size analyses were executed. With time, conversion to crystalline form occurred and, in four days, the amorphous content decreased from 47% (w/w) to 8.7% (w/w). In conjunction with this decrease, water content decreased (the amorphous form is more hygroscopic) and particle size increased.

The problems did not occur with the alternative process of HPH followed by spray-drying. (SD). Figure 5 shows the XRPD traces (in the region 12.0-16.5 º 2θ) of the non-micronized material, of a 5% (w/w) reference mixture (95% (w/w) crystalline + 5% (w/w) amorphous) and of a sample obtained via HPH + SD. No difference is detected, in terms of baseline, between this result and the 100% crystalline powder. The data indicates that the amorphous content is well below 5% (w/w). Based on this data, stable FP solid Form I can be produced by this technology.

Moreover, HPH + SD may allow control of particle size and the production of powders with tighter PSDs than a traditional micronization process. It also may enable greater flexibility in achieving multiple particle size values and tight ranges allowing for customization of particles, depending on the inhalation delivery system in use, as observed in Table 1 for different FP batches.

In developing generic inhalation products, formulators need to guarantee that the API particles have the same morphology of the innovative product and can therefore maintain the aerodynamic characteristics so critical in obtaining a bioequivalent profile. Scanning electronic microscopy (SEM) data (Figure 6) shows that particle morphology obtained by HPH and jet

Table 1

Particle size values of four batches of FP processed by HPH + SD.

Fluticasone Propionate	d(0.1) (µm)	d(0.5) (µm)	d(0.9) (µm)	Span
I	1.63	3.56	8.98	2.1
II	1.40	3.05	6.94	1.8
III	1.20	2.45	4.68	1.4
IV	0.79	1.70	3.39	1.5

$$\text{Span} = \frac{D[v, 0.9] - D[v, 0.1]}{D[v, 0.5]}$$

Figure 3

XRPD patterns of non-micronized FP Form 1 (a), micronized first pass (b), micronized second pass (c) and amorphous (d).

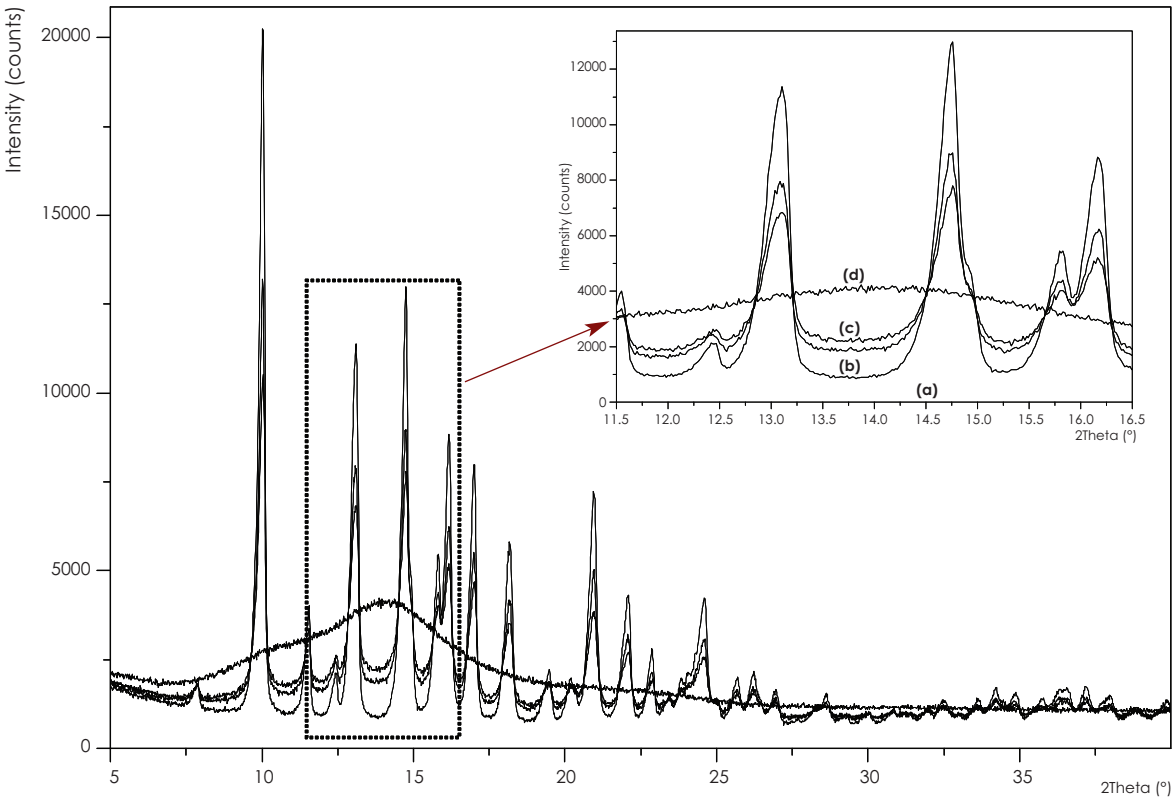
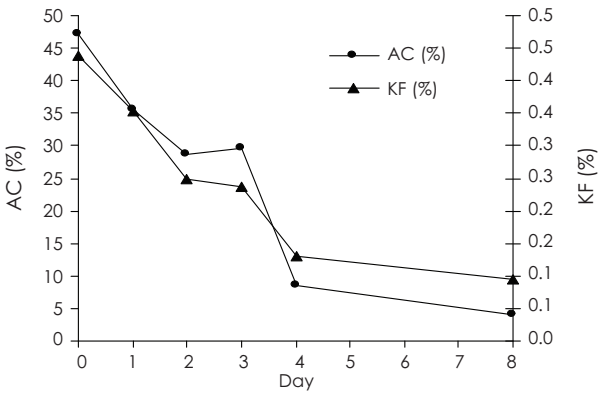
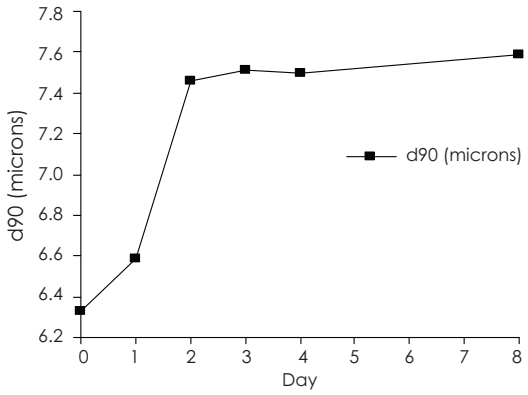


Figure 4

Amorphous material, water content and particle size, at room conditions, measured as a function of time.



(a) Amorphous (●) and water (▲) content over time after single pass micronization.



(b) Particle size (d90) (■) over time after single pass micronization.

mill micronization are similar. This supports the premise that this novel technology is an alternative to conventional air jet milling and is able to maintain the relevant physical characteristics required for developing a bioequivalent drug product.

Mometasone Furoate Monohydrate

Mometasone furoate monohydrate (MFM) is a synthethic corticosteroid, used as a nasal suspension spray and indicated for the treatment of nasal symptoms of seasonal allergic and perennial allergic rhinitis.

MFM was prepared by the addition of water to a saturated solution of anhydrous mometasone furoate in acetone. Crystals of the monohydrate were collected by filtration and dried. The water content obtained by Karl-Fisher titration of the products (720 KFS Titrino, 703 Ti stand, Metrohm) was between 3.00 and 3.78% w/w. XRPD, IR and DSC analyses were consistent with mometasone furoate monohydrate. X-ray powder diffraction showed that the isolated product was 100% crystalline monohydrate material.

In a nasal suspension, the PSD d(0.9) target is below 10 µm, which is generally produced in the industry by micronization. The changes in MFM were studied, specifically hydration level under air jet milling versus HPH.

The product was micronized in three consecutive runs. The particle size of the product, as measured by laser diffraction (Mastersizer 2000 equipped with a Hydro 2000S dispersion cell, Malvern Instruments Ltd.) decreased during each run. In conjunction the water content, measured by Karl-Fischer titration, decreased as well. This is related to loss of water by crystallization, due to the high surface temperatures that occur during mechanical milling[6]. These results are presented in Table 2.

Table 2

Particle size distribution and water content by KF determined in the product micronized by air jet milling.

	Particle Size Distribution Results			Water Content by KF (% w/w)
	d(0.1) (µm)	d(0.5) (µm)	d(0.9) (µm)	
Starting Material	4.3	27.5	63.4	3.38
1st Passage	1.9	5.7	17.5	3.00
2nd Passage	1.4	4.2	8.7	2.56
3rd Passage	1.5	3.6	7.7	2.91

When MFM was subjected to particle size reduction by HPH followed by spray-drying, the water content of the isolated products was within the theoretical water percent (Table 3). The particle size of the isolated products was similar to that obtained with micronization. HPH + SD is able to produce MFM of high crystalline purity (high monohydrate content) with a particle size suitable for nasal applications.

Table 3

Particle size distribution and water content by KF determined in the product subject to HPH + SD.

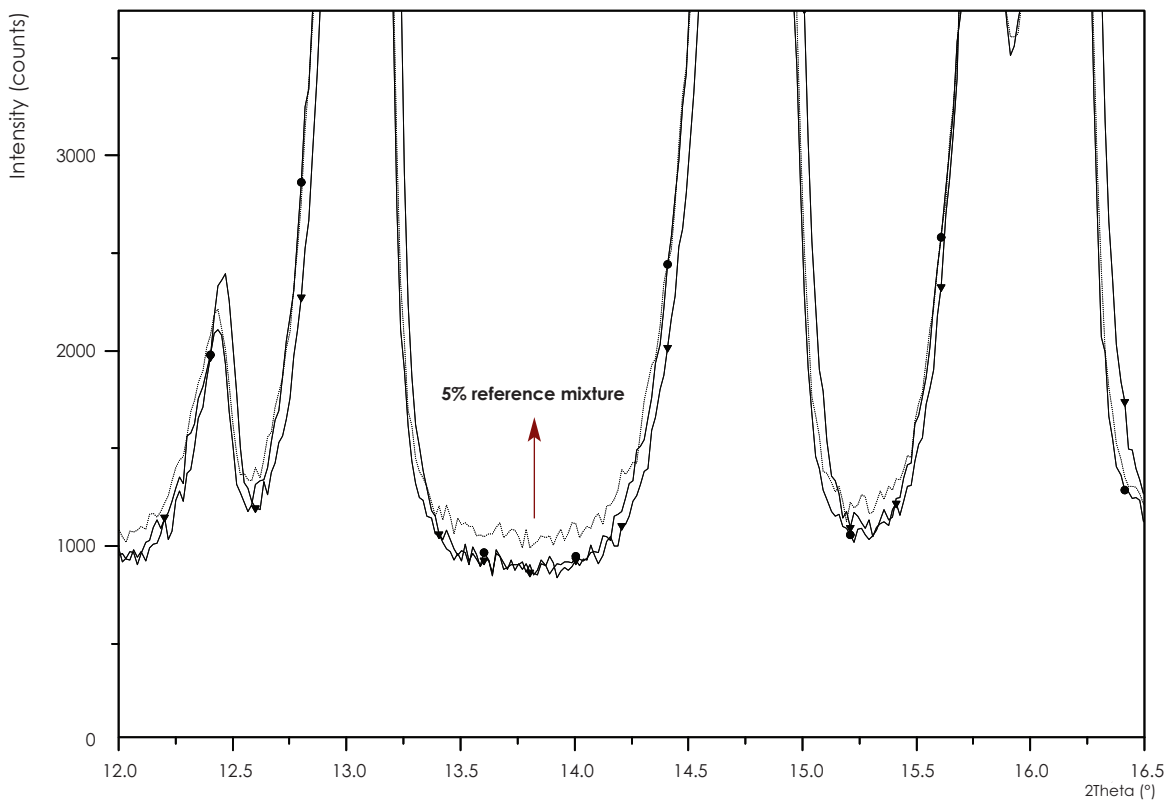
Particle Size Distribution Results			Water Content by KF (% w/w)
d(0.1) (µm)	d(0.5)(µm)	d(0.9) (µm)	
1.81	4.05	8.08	3.47
0.97	2.8	6.55	3.26

Conclusions

The aerodynamic particle size distribution of APIs used to formulate DPI and MDI products for inhala-

Figure 5

XRPD patterns of non-micronized FP Form 1 (▲), processed by HPH + SD (●) and a 5% (w/w) amorphous reference mixture (---).



tion is a critical factor in the subsequent performance and registration of the finished product. Therefore, the process of producing such APIs is also critical.

In these case studies, the alternative size reduction process of high pressure homogenization followed by spray drying, when compared to the current industry norm of micronization, has been shown to:

- produce a much lower amorphous content (<5% than standard micronization (≈45% and variable), therefore indicative of better long term stability and likely to enable an easier registration review process for the finished product; this is relevant for nasal suspensions as well as inhalation products
- provide a greater control of particle size (more efficient process with closer control of target particle size and narrower size distribution)
- maintain the same polymorphic form of API and level of hydration

In summary, this alternative size reduction process, available from Hovione, has proven benefits compared to air jet milling in providing inhaled grade APIs for DPI, MDI and nasal finished products.

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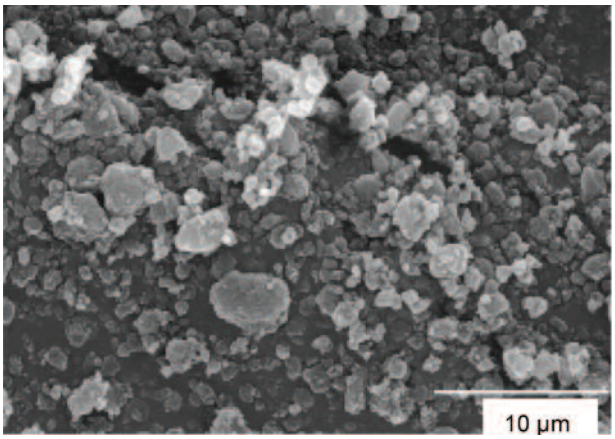
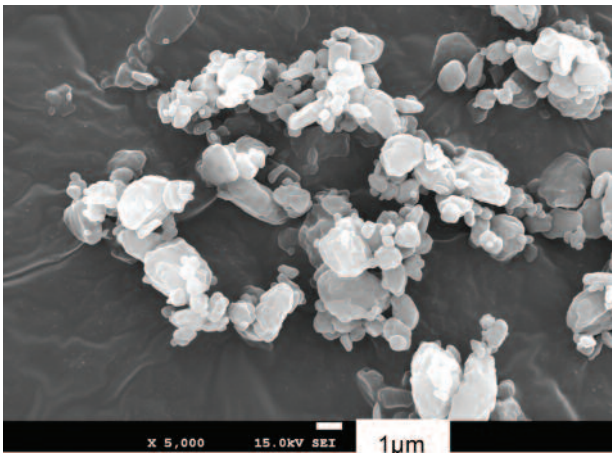
Figure 6

Scanning electronic microscopy (SEM) data shows particle morphology obtained by HPH and jet mill micronization are similar. Note: scales are different.



(a) FP micronized by conventional air jet milling.



(b) FP micronized by HPH + SD.

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*Amorphous content was determined by an XRPD method developed and fully validated for the determination of low amounts of amorphous material (below 10%) in crystalline FP. System suitability, using a 5% mixture of amorphous in crystalline FP, is always measured (three determinations) prior to each analysis. As acceptance criterion, it was defined that the predicted amorphous concentration of this reference mixture should lie within a 10% margin (+/-10%) of the true concentration.