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Influence of the Storage Orientation on the Aerodynamic Particle Size of a Suspension Metered Dose Inhaler Containing Propellant HFA-227

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ABSTRACT

Presented in this work are the results of a study designed to investigate the impact of the storage position on the particle size distribution (PSD) of a steroid suspension metered dose inhaler (MDI) containing propellant HFA-227. It was hypothesized that the orientation of MDI samples upon storage could influence the PSD of the emitted dose, since it determines the amount of contact the liquid formulation has with the valve and therefore the quantity of nonvolatile leachable materials from the valve components that may enter the product and potentially impact the aerosol spray dynamics. Samples stored in the valve down orientation (i.e., complete contact of the liquid formulation with the valve) showed a higher level of leachables compared to those samples stored valve up (i.e., minimal contact of the formulation with the valve). The valve down samples were found to produce larger particles in the emitted aerosol spray using both cascade impaction, the preferred method of regulatory submission, as well as laser diffraction. It was postulated that the larger particle size of the inverted samples was attributed to its higher levels of leachables. Based on our findings, it is recommended that in order to set appropriate controls on the product PSD, the storage orientation of the product will need to be considered.

Key Words: Cascade impaction; Laser diffraction; Particle size; Metered dose inhalers; Storage orientation; Leachables.

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INTRODUCTION

A metered dose inhaler (MDI) is the most commonly used device for delivering drugs to the respiratory tract in the treatment of pulmonary diseases such as asthma.[1–3] The MDI device, comprised of the formulation, a metering valve, container (can), and actuator, is delivered to the patient as an aerosol of fine droplets by the atomization of the liquid phase of the formulation. The driving force for atomization is provided by the evaporation of the propellant within the actuator nozzle.[4,5–10] In most marketed products, the drug, which is micronized, is added to a propellant/surfactant mixture to produce a suspension formulation.

The aerodynamic particle size distribution (PSD) of the product is a critical parameter that needs to be carefully controlled since it determines where the aerosol will deposit in the respiratory tract and is closely linked to the efficacy as well as the side effects of the delivered medication.[11–14] Aerosol droplets that are $\leq 5\,\mu m$ in diameter are considered respirable and have the highest probability of reaching the lower respiratory tract. Medications used for local treatment of the lung, i.e., beta-2 agonists for bronchodilation or corticosteriods for the reduction of inflammation caused by asthma, generally target the size range of 2–5 μm.

As a result of the importance of controlling the particle size of the delivered dose of MDIs, this study was initiated to evaluate the influence of storage position on the PSD of a suspension aerosol containing propellant HFA-227. During patient handling, the MDI can be stored valve down (inverted), valve up (upright), or with the unit on its side. Thus, it is important to understand any impact of storage orientation of the MDI device on product performance.

It was hypothesized that the PSD could be affected by the storage orientation since the MDI storage orientation determines the amount of contact the liquid formulation has with the valve components and thus the potential for materials from the valve components to dissolve or leach into the product. These leachable materials, which are nonvolatile, could then contribute to a change in the mass median aerodynamic diameter (MMAD) and the fine particle dose (FPD) of the product by interacting with the drug and/or reducing the spray evaporation rate. It was anticipated that a product stored valve down (inverted—maximum contact of the liquid formulation with the valve components) would exhibit a greater change in the particle size over time compared to being stored valve up (upright–minimum contact of the liquid with the valve components).

Due to the imminent phase-out of CFC propellants and replacement with HFA propellants in new MDI formulations,[14,15] a model HFA formulation was chosen for this work. Since HFA propellants possess different physical and chemical properties than CFC propellants[2,16–19] and also new elastomeric valve materials are being used with the HFA MDI formulations,[18] it was deemed critical to evaluate the performance of this model HFA formulation.

Based on the large breadth of stability data (generated at ICH room temperature and accelerated conditions) on our HFA-based formulations, it was not expected that factors such as moisture ingress, weight loss, and particle growth would be influenced by the storage position. Moisture levels were found to be the same for samples stored in the upright and inverted orientations for these formulations. Weight loss for these HFA formulations were found to be insignificant ($< 0.1\%$/year). No qualitative difference in particle shape or size with storage orientation was found in the microscopic evaluation of the suspended drug substance of these formulations.

MATERIALS AND METHODS

Preparation of Samples

A single batch of a suspension product containing micronized drug (corticosteriod, about 1 μm median diameter), a surfactant (long-chain fatty acid), alcohol (ethanol), and propellant HFA-227 was manufactured according to a standard method for the manufacture of aerosol products. The alcohol level used in the batch was less than 5% w/w. The combined drug and surfactant levels used in the batch were less than 0.2% w/w. About 16 g of the suspension was filled into a commercially available 14-mL aerosol can and crimped with a 63-μL valve, typically used with metered dose inhalers.

The batch was filled into two sub-lots with each sub-lot containing a different valve lot. The valve lots were comprised of identical components and only differed in the elastomer used. The properties of these elastomers covered the supplier's normal range. These sub-lots are referred to as B17 and B21.

Immediately following batch manufacture, all samples were stored in the valve down position for a period of about 4 weeks at ambient room temperature conditions. For this study, samples were then

stored at the ICH accelerated condition (i.e., 6 months at 40°C/75% relative humidity (RH)). Within each sub-lot, half the samples were stored in the valve up (upright) orientation and the other half were stored in the valve down (inverted) orientation. The visual inspection of the suspension at these storage conditions revealed the tendency of the drug to settle in the bottom half of the suspension medium with no detectable creaming. Microscopic evaluation (scanning electron microscopy using a Hitachi S-3500N, Hitachi high technologies, Gaithersburg, MD, 5 kV accelerating voltage) of representative samples stored for 6 months at 40°C/75% (RH) confirmed the absence of any qualitative size or shape differences for the suspended drug substance between upright and inverted storage.

Leachable Testing

Upon completion of the storage time, leachable testing was conducted on a composite of five cans for each sub-lot/orientation. The known leachables were characterized and quantified using validated HPLC and GC methods. The residual standard deviation (RSD) for this method was typically $\leq 5\%$.

Cascade Impactor Testing

The particle size was initially evaluated using cascade impaction, the method required by the FDA for size classification of MDIs. This methodology, well documented in the literature,[20–22] provides a measurement for the PSD of the droplets associated with the drug.

The Mark II Andersen Cascade Impactor (1 AFCM Non-Viable Ambient Particle Sizing Sampler, 28 L/min flow rate, Graseby-Andersen, Smyrna, GA) was used to obtain the PSD of the aerosol spray droplets associated with drug. A 1-liter glass entry port was employed in place of the USP entry port since studies in this laboratory have shown it to provide more sensitivity to changes in particle size of the suspended drug substance than the latter entry port.[23] Each sample was fitted with a standard actuator for oral delivery and tested as per a validated cascade impaction method. The sample was primed prior to testing. The experimental design involved sampling two sprays from each inhaler with three cans for each sub-lot/orientation tested.

The drug was recovered from the cascade impactor stages and accessories in an appropriate solvent (HPLC grade), and the concentration determined via high-performance liquid chromatography with spectrophotometric detection. The mass of drug on each stage or accessory was divided by the total amount collected to give the percent of dose for each stage of the apparatus. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were estimated based on the USP method.[22] The fine particle dose, also calculated, is defined as the percent of the dose $\leq 4.7\,\mu m$.

Sympatec Testing

The particle size was also evaluated using laser diffraction, a more exploratory method (i.e., not required by the FDA) for size classification of MDIs. This methodology, which is described in the literature,[24–26] provides a combined distribution of the droplets associated with the drug as well as the droplets that are not associated with drug (i.e., contain propellant alone or with other nonvolatile ingredients).

The Sympatec HELOS Compact, model KA with a R2 helium-neon laser (0.25–87.5 microns) was used to obtain the PSD, referred to as the volume size distribution (VSD), of the aerosol spray droplets (Sympatec, GmbH, Windox Software 3.0, Clausthal-Zellerfeld, Germany). A special adapter for which MDI actuation could be performed automatically was attached. According to this method,[24–26] a detector with 31 channels is used to measure the diffraction pattern caused by the presence of particles in the path of the laser beam. The measurement begins after the first few spray droplets pass through the laser beam and stops when the spray decays below a detectable level. Fraunhofer diffraction is used as the mathematical theory for assigning the measured diffraction intensity to the particle size and frequency. The diameter of the diffraction ring is inversely proportional to the size of the particles, while the distribution of the light energy in the diffraction pattern is associated with the particle quantities. All particles present in the measured cross section transmit scattered light to create the diffraction pattern. The software converts the light scattering information to a VSD, i.e., the volume distribution of particles present in individual size classes.

The VSD profile was obtained at a spray distance of 18 cm (measured from the actuator mouthpiece) for the B17 and B21 sub-lots. Based on preliminary screening of the aerosol plume length, it was decided

that the droplets emitted at this distance would provide a good representation of the product. The experimental design involved sampling two sprays from each inhaler with three cans for each sub-lot/orientation tested at each distance.

RESULTS AND DISCUSSION

1. Impact of Storage Orientation on Leachables

The results show that sample orientation at the ICH accelerated condition, i.e., 6 months at 40°C/75% RH, has an impact on the leachable level (for UV detectable material; Table 1). This is reflected in both the B17 and B21 sub-lots by the fact that the samples stored in the inverted position have approximately a 30% higher leachable level than those stored in the upright position (Table 1).

Furthermore, there is low variability in the leachable levels between different valve lots of this rubber composition (i.e., that of B17 and B21 sub-lots). The values for the upright samples of B17 and B21 sub-lots are comparable (362 and 360 μg/unit, respectively, Table 1) as are the inverted samples for B17 and B21 sub-lots (570 and 520 μg/unit, respectively, Table 1).

It is not surprising that the leachable levels are higher for the inverted samples relative to the upright samples (Table 1). For samples stored in the inverted orientation, the liquid phase of the formulation is in constant contact with the valve components, whereas for the samples stored in the upright orientation, the liquid contact with the valve components is minimal. Therefore, for the inverted samples, materials from the valve components (i.e., inorganic fillers, curing agents, plasticizers, lubricants, and antioxidants) that are soluble in the formulation[27,28] have a greater probability of dissolving in the formulation.

Table 1. Summary of leachable results.

Sub-lot	Orientation	Total nonvolatile leachables,[a] μg/unit
B17	Inverted	570
	Upright	362
B21	Inverted	520
	Upright	360

[a]Composite of 5 cans for each sub-lot.

The presence of some leachable material in the upright samples (Table 1) is likely due to the fact that, prior to storage of these samples at the 40°C/75% RH condition, the upright samples were stored inverted for about 4 weeks (see Materials and Methods section). Storage at these conditions could have resulted in valve materials entering the product.

The leachable levels may have been enhanced by the presence of the cosolvent ethanol, typically used in HFA formulations.[18] Although for this model HFA system, the rubbers are cleaner than those previously used with CFC formulations,[27,28] the presence of cosolvents such as ethanol in HFA formulations may increase the solubilization of the leachables in the liquid phase.[18] This is especially true when samples are stored in the inverted position. This could lead to a greater contribution of leachables as a formulation contaminant.

2. Impact of Storage Orientation on Particle Size by Andersen Cascade Impaction

Drug Recovery

The total drug recovered on the cascade impactor stages and accessories for B17 and B21 sub-lots was close to label claim (LC) for the upright samples (>94% LC) and was reduced to about 10% below LC for the inverted samples (Table 2).

It was observed qualitatively that for the inverted samples, a portion of the drug was found to be adhering to the can wall whereas for the upright samples, drug can wall adhesion was negligible. The observation of drug on the can wall for the inverted samples is consistent with the lower amount of drug recovered in the impactor for these samples (Table 2), since the drug that has adhered to the can wall would be unavailable for delivery in the emitted spray.

Table 2. Percent of label claim (LC) of active recovered in the cascade impactor.

Sub-lot	Orientation	% LC of active recovered,[a] mean ± SD
B17	Inverted	88.0 ± 2.5
	Upright	96.3 ± 2.5
B21	Inverted	84.7 ± 4.9
	Upright	94.2 ± 2.0

[a]Described in the experimental section, N = 3.

It appears that the higher can wall adhesion of the samples in the inverted position is related to the extended contact of the valve components with the suspension medium as well as the suspended drug (in which a portion tends to settle). This may lead to a greater potential for the leachables to adhere to the can wall and/or the surface of the drug, affecting their surface properties in such a way as to enhance the can wall adhesion of drug.

Impactor Recovery

The overall recovery of the dose on the impactor stages, entry port, and casings appears to be relatively insensitive to sample orientation as shown by the comparable results for the percent of dose collected for the inverted and upright orientations of the B17 and B21 sub-lots (Table 3). This suggests that the percent of dose that reaches the impactor (i.e., percent of dose $< 10\,\mu m$) is not highly dependent of the storage orientation. In all cases, greater than 80% of the dose was collected on the impactor stages (Table 2).

Aerodynamic Particle Size Distribution

The PSD profiles obtained by cascade impaction, which measures the distribution of particles associated with drug that are $< 10\,\mu m$, reflects a larger particle size and broader distribution for the inverted samples compared to the upright samples. The PSD profiles show that inverted samples have a greater proportion of dose on the upper stages (larger particles) relative to the lower stages (smaller particles; Fig. 1). This is evident by the $\approx 20\%$ reduction in fine particle dose (percent of dose less than $4.7\,\mu m$) for the inverted samples compared to the upright samples (Table 3).

Similarly, the impact of orientation on the aerodynamic particle size is reflected in both the MMAD and GSD parameters. The MMAD, calculated from these aerodynamic PSDs, is 0.4–0.5 μm larger for the inverted samples compared to the upright samples (Table 4). In addition, the distribution is broader for the inverted samples as reflected by the larger GSD values (Table 4).

As with the leachable results (Table 1), there is little variability in these PSD results among samples that contain the different valve sub-lots. Thus, in a given orientation, the results for the B17 and B21 sub-lots are comparable (Fig. 1, Tables 3 and 4).

3. Impact of Storage Orientation on Particle Size by Sympatec

The volume size distribution (VSD) and cumulative size distribution of the emitted spray droplets obtained by Sympatec at the 18 cm spray distance for the upright and inverted samples of sub-lots B17 and B21 are given in Figs. 2 and 3, respectively. The VSD profiles are presented as a frequency distribution based on volume (log of density %).

The Sympatec VSD distribution curves (Fig. 2) reflect a bimodal distribution for both the upright and inverted samples. This is in contrast to the cascade impactor PSD profiles (Fig. 1) in which only a single maximum was observed.

The cumulative volume size distribution (VSD) of the emitted spray droplets (cumulative % of density) show that overall, the upright samples appear to have a higher percentage of droplets under $10\,\mu m$ (Fig. 3). This is consistent with the higher % of fine particles and smaller MMAD observed for the upright samples from the cascade impactor testing (Tables 3 and 4, respectively).

However, the VSD profiles (Figs. 2 and 3) show a higher proportion of small droplets ($< 5\,\mu m$) for the

Table 3. Percent of drug in emitted dose on impactor stages and accessories.

		% Drug recovered from dose[a], mean ± SD			
Sub-lot	Orientation	On impactor stages	On entry port	On casings	As fine particles (< 4.7 μm)
B17	Inverted	82.5 ± 0.3	10.9 ± 0.3	6.7 ± 0.5	44.9 ± 3.0
	Upright	85.6 ± 1.2	8.5 ± 1.0	5.8 ± 0.3	55.3 ± 3.4
B21	Inverted	83.1 ± 2.0	9.7 ± 1.4	7.2 ± 0.9	43.9 ± 1.5
	Upright	85.7 ± 3.0	8.6 ± 2.7	5.7 ± 0.2	54.8 ± 1.3

[a]Described in the experimental section, N = 3.

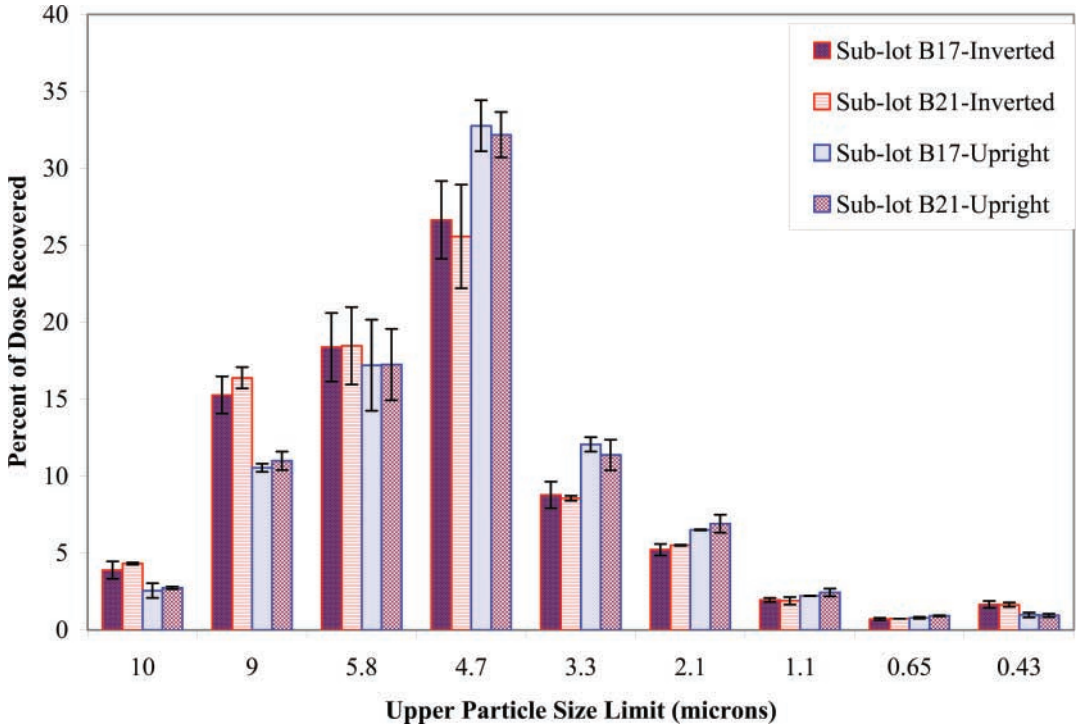

Figure 1. Andersen cascade impactor PSD profiles for sub-lots B17 and B21 in the two storage orientations.

Table 4. Estimated values for MMAD and GSD[a].

Sub-lot	Orientation	MMAD, μm[b] mean ± SD	GSD[b] mean ± SD
B17	Inverted	3.75 ± 0.15	2.36 ± 0.08
	Upright	3.34 ± 0.05	2.11 ± 0.03
B21	Inverted	3.84 ± 0.07	2.39 ± 0.03
	Upright	3.35 ± 0.04	2.13 ± 0.03

[a]Estimated based on USP method.
[b]N = 3.

inverted samples relative to the upright samples, which was not predicted from the cascade impactor data. It is likely that most of the droplets in the first high density region of the VSD profile (around 1.4 μm, Fig. 2), represent the drug-free droplets containing mostly propellant HFA-227 with small amounts of other nonvolatile components in the formulation (i.e., surfactant and alcohol). The droplets in this region are probably too small to contain drug since most of the drug particles are at least 2 μm in diameter (as determined by microscopic examination).

Based on the assumption that the peak around 1.4 μm represents essentially drug-free droplets, then the contribution of drug-free droplets is greater for the inverted samples since the 1.4 μm peak height is larger (Fig. 2).

The other high density region of the VSD profile (around 6.8 and 8.0 μm, respectively, for the upright and inverted samples, Fig. 2), could be comprised of both drug-free and drug-containing droplets. It is believed that the droplets of this size do not necessarily have to contain drug, since a separate study in our laboratory with the corresponding placebo batch of this formula revealed that drug-free droplets can also appear in a 5–10 μm region.

4. Impact of Storage Orientation on Formulation Properties

A plausible reason for the larger aerodynamic PSD of the drug-containing particles (cascade impaction results) of the inverted samples is the enhanced aggregation of the drug particles. It is hypothesized that upon inverted storage, the chemical properties as well as the quantity of valve materials that are present in the formulation can cause

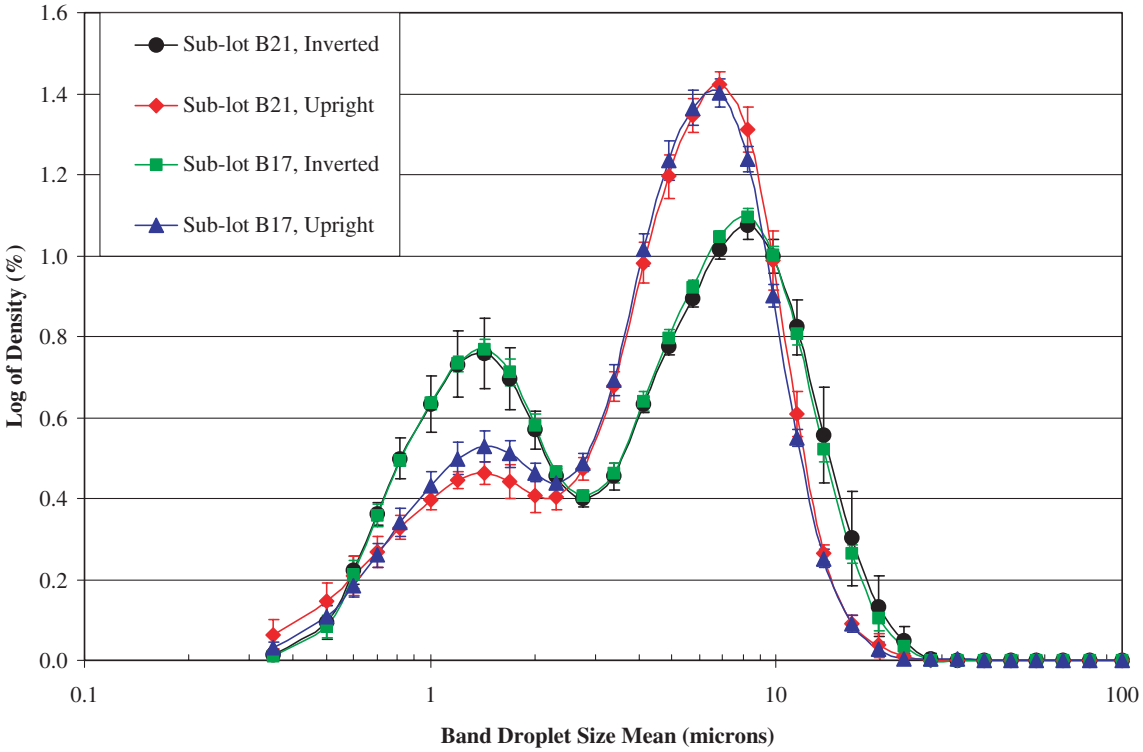

Figure 2. Sympatec VSD profiles for sub-lots B17 and B21 in the two storage orientations.

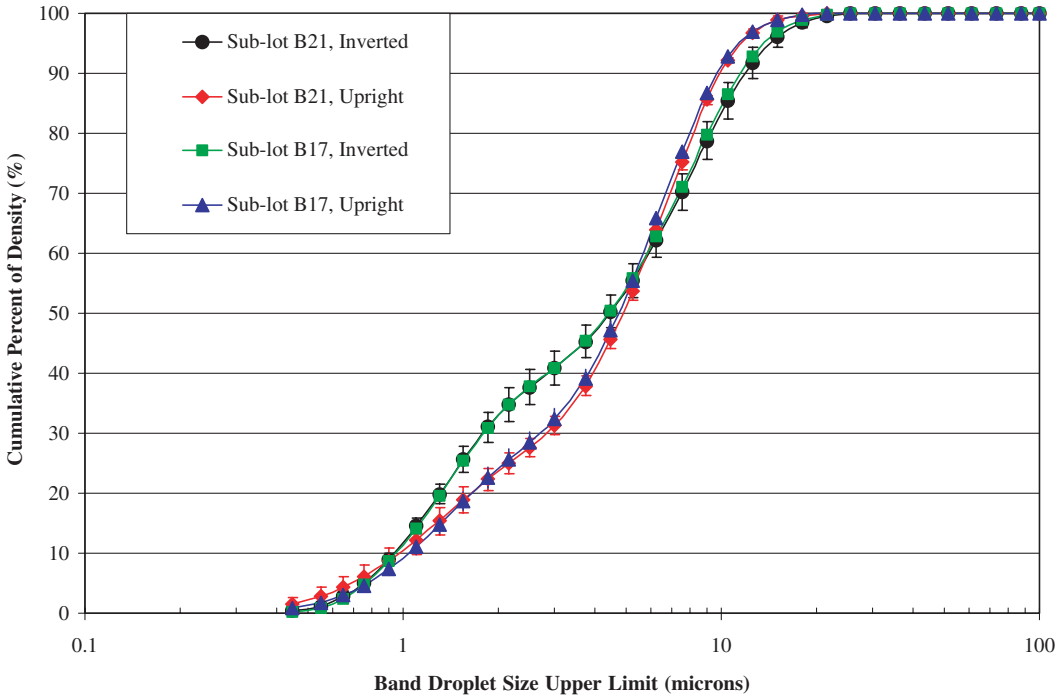

Figure 3. Cumulative Sympatec VSD profiles for sub-lots B17 and B21 in the two storage orientations.

significant interparticle attraction that can lead to a larger aerodynamic particle size.

For suspension formulations, it has been found that formulation additives, by altering the surface properties of the drug, can often promote drug aggregation and lead to an increase in the aerodynamic particle size of the product.[31] Although the exact nature of the interaction of the leachables with the formulation is still under investigation at this time, it is assumed that the surface properties of the suspension were affected by the leachables since the can wall adhesion was substantial only in the inverted orientation.

It has also been found that a reduction in the droplet evaporation rate can lead to an increase in the aerodynamic particle size.[10,29–32] This may be a factor, although it probably does not entirely explain the increase in aerodynamic particle size for the inverted samples. The levels of leachables that were detected in the samples are very low ($< 0.1\%$ w/w) and it is not anticipated that these levels could contribute in any significant measure to the evaporation rate of the emitted spray droplets. This needs further investigation since a complete elucidation of the chemical properties of the leachables is a complex matter.

It is postulated that the higher proportion of small droplets for the inverted samples (VSD profiles; Figs. 2, 3) is a consequence of the higher concentration of drug particles per droplet, i.e., as a result of greater interparticle attraction. This could lead to fewer drug droplets. At the same time, the remainder of the emitted spray would be comprised of smaller, drug-free droplets. Since the VSD profile is comprised of both drug and drug-free droplet distributions, then it is plausible that the inverted samples that contain larger drug droplets simultaneously show a larger cumulative amount of drug-free particles in the region $< 5\,\mu m$ (Figs. 2, 3).

The fact that the presence of nonvolatile ingredients can produce droplet sizes that are smaller than that of drug has been reported in studies with the QCM impactor, which uses piezoelectric quartz crystals as mass sensors on the QCM plates.[33] As in the laser diffraction method, the QCM measures the size distribution of the drug along with any nonvolatile excipients, so the PSD is made up of both drug particles and nonvolatile excipients. A reduction in droplet size was obtained for formulations in which non-volatile ingredients were added, suggesting that the nonvolatile distribution was finer than that of the drug and caused the overall distribution to shift to a finer PSD.[33]

CONCLUSION

It is concluded from this work that storage orientation can have an impact on the PSD profile of MDIs. This may be related to differences in the chemical interactions of the leachables found for samples stored in different orientations. In the inverted position, where there is maximum contact of the product contents with the valve components, leachables are found to be highest and the drug PSD profile shows generally larger particles for samples stored in this position compared with samples stored in the upright position. Since it is critical that the drug PSD of MDIs be tightly controlled, it is important that all factors that affect it be well understood.

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