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RESEARCH PAPER

Influence of the Valve Lubricant on the Aerodynamic Particle Size of a Metered Dose Inhaler

Julianne Berry, Ph.D.,* Lukeysha Kline, B.A., Venkatesh Naini, Ph.D., Saeed Chaudhry, M.S., John Hart, Ph.D., and Joel Sequeira, Ph.D.

Schering Plough Research Institute, Kenilworth, New Jersey, USA

ABSTRACT

Presented in this work are the results of a study designed to investigate the impact of valve lubricant (i.e., silicone oil) on the aerodynamic particle size distribution (PSD) of a steroid suspension metered dose inhaler (MDI) containing propellant HFA-227. The objective of this study was to explore whether the valve lubricant, which is often used in MDI products to prevent valve sticking, can enter an MDI product and potentially impact the aerosol spray dynamics. The results of this work have shown that samples containing valves with high silicone levels produced a larger aerodynamic particle size (by cascade impaction) than samples with low-silicone or silicone-free valves. It is postulated that the presence of silicone in the product may increase the propensity for drug aggregation, thereby leading to an increase in the aerodynamic particle size of the emitted aerosol. These findings stress the importance of evaluating the effects of valve lubricant on the aerodynamic PSD in the early formulation development stage of an MDI.

Key Words: Cascade impaction; Laser diffraction; Particle size; Metered dose inhalers; Valve lubricant.

INTRODUCTION

Metered dose inhalers (MDIs) are the most widely used devices for delivering drugs to the respiratory tract in the treatment of pulmonary diseases such as asthma and chronic obstructive pulmonary disease.[1–3] The MDI delivery system, comprised of the formulation, metering valve, container (can), and actuator, is used to administer a fine droplet spray, formed when the pressurized formulation is sheared and atomized after exiting the actuator orifice. Most currently marketed products are suspensions that contain micronized drug suspended in a propellant/surfactant mixture that forms primary drug particles or particle

*Correspondence: Julianne Berry, Ph.D., Schering Plough Research Institute, 2000 Galloping Hill Rd., Kenilworth, NJ 07033, USA; E-mail: julianne.berry@spcorp.com.

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agglomerates inside the emitted droplets upon actuation of the MDI.

The aerodynamic particle size distribution (PSD) of the emitted aerosol plume is a critical parameter, since it determines regional deposition in the respiratory tract and is closely linked to efficacy as well as side effects of the delivered medication.[4–7]

The operation of the MDI device involves movement of the valve stem through a gasket. Upon actuation, this movement releases the dose from the metering chamber to the actuator. In order to prevent the stem from sticking (and thus delivering a suboptimal dose), a lubricant is usually applied to the valve stem and/or valve seals that are in contact with the stem. For most commercial MDI valves, food grade silicone oil is employed as the lubricant.

Since a potential exists for valve lubricant entry into the product both during manufacturing (i.e., pressure filling through the valve) and storage, this work is presented in an effort to explore the influence of silicone oil valve lubricant on the aerodynamic PSD of a suspension aerosol containing propellant HFA-227. Due to the imminent phase-out of chlorofluorocarbon (CFC) propellants and replacement with hydrofluoroalkane (HFA) propellants in new MDI formulations,[7,8] a model HFA formulation was used for this purpose.

MATERIALS AND METHODS

Sample Description

An outline summarizing the batches presented in this work is given in Table 1. The test formula, an MDI suspension, was comprised of micronized drug (corticosteriod), a surfactant (long-chain fatty acid), alcohol (ethanol), and propellant HFA-227. Two lots of micronized drug substance (lots 1 and 2) were utilized in this study as specified in Table 1. The median particle size of drug substance lots 1 and 2 were 1 μm and 1.5 μm in diameter, respectively. The alcohol level was less than 5% w/w. The combined drug and surfactant levels were less than 0.2% w/w. The product fill weight was ≈16 g.

Table 1. Summary of batch information.

Batch	Drug substance	Manufacturing method	Sub-lot	Valve description
1	Lot 1	1-Stage (I)	A	Low silicone
			B	High silicone
2	Lot 2	1-Stage (I)	A	Low silicone
			B	High silicone
3	Lot 1	2-Stage (II)	A	Low silicone
			B	High silicone
			C	Silicone free

The packaging components consisted of a 14-mL aerosol can and 63-μL valve, specifically designed for use with MDIs. The valve description (Table 1) was based on the level of lubricant applied by the manufacturer. The valves were divided into the following categories: the low-silicone valve, the high-silicone valve, and a silicone free valve.

Independent studies had shown that silicone lubricant that was employed in the valve was insoluble in the liquid component of this model formulation and that the drug was also found to be insoluble in the lubricant. In addition, the formulation moisture level, valve delivery (i.e., shot weight), and force of actuation were not affected by valve silicone level.

The level of silicone in the valve was measured using an established infrared (IR) procedure that was based on the comparison with the reference pattern of the lubricant standard. The level of silicone found in several representative valves from each of the above categories was ≈50, ≈350, and 0 μg/valve, respectively, for low-, high-, and silicone-free valve types. For representative product samples containing the high silicone valves, a detectable level of silicone (≈140 μg) was found in the can contents. For representative product samples containing the low- and silicone-free valves, the silicone in the can contents was found to be below a detectable level (<20 μg).

The test samples (Table 1) were manufactured by either of two standard methods. In the first method (one-stage; Method I), the entire suspension product was compounded within about 1 hour and then filled in one step through the valve of an empty crimped can/valve assembly. In the second method (two-stage; Method II), the bulk drug concentrate was mixed for >24 hours and then added to an open can. The can containing the concentrate was subsequently crimped with a valve and filled with propellant through the valve. Independent studies in this laboratory had shown that Method I was found to produce a suspension with a significantly smaller particle size to that of Method II. Upon completion of batch manufacturing, all samples were stored at controlled room temperature and humidity conditions [≈20° C, 40% relative humidity (RH)] in the valve down orientation prior to testing. Batches 1 and 2 (Table 2) were tested within 2 weeks of batch manufacture and Batch 3 was tested after aging for >2 weeks. Note that independent studies

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

Batch	Sub-lot	Valve description	% LC of active recovered
1[b]	A	Low silicone	100±2
	B	High silicone	100±3
2[c]	A	Low silicone	94.3±3.7
	B	High silicone	82.0±10.0
3[d]	A	Low silicone	104±8
	B	High silicone	103±4
	C	Silicone free	101±4

[a]Described in the experimental section, average and standard deviation values reported.
[b]N=six samples.
[c]N=three samples.
[d]N=two samples; each sample tested three times.

had shown that the formula used in this work is stable within the time of testing and therefore the test date was not considered significant.

The product was also filled into glass MDI containers containing the high- and low-silicone valves and visually inspected (qualitative only) for differences in suspension properties. In addition, MDI samples were prepared with silicone spiked into the product at levels ranging from below to above the manufacturers' range typically found in the valve. The latter samples were compared with those that were free of spiked silicone (i.e., standard formulation).

Cascade Impactor Testing

The aerodynamic particle size was evaluated for representative active samples described in Table 1 using cascade impaction, the method required by the Food and Drug Administration (FDA) for the size classification of MDIs. This methodology is well documented in the literature[9–11] and provides an aerodynamic PSD of the droplets and/or particles associated with the drug. A Mark II Andersen cascade impactor (1 AFCM Non-Viable Ambient Particle Sizing Sampler, Graseby-Andersen, Smyrna, GA) was used at 28.3 L/min airflow. A 1-liter glass entry port was employed in place of the United States Pharmacopeia (USP) throat since studies in this laboratory have shown it to provide more sensitivity to changes in particle size than the latter entry port.[12] Each sample was fitted with an oral actuator and sprayed two times into the cascade impactor. Testing was performed as per a validated cascade impaction method. All aerosol cans were primed with a minimum of two actuations prior to testing.

The drug was recovered by washing the cascade impactor stages and accessories in an appropriate solvent, and the concentration determined using high-performance liquid chromatography (HPLC) 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 recovered in each part of the apparatus. The mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were estimated based on the USP method.[11] The fine particle dose was defined as the percent of the dose $\leq$4.7 μm. The unpaired Student's t-test was used for statistical evaluation of the results.

Laser Diffraction Droplet and Particle Sizing

A Sympatec HELOS Compact, Model KA (Sympatec GmBH, Clausthal-Zellerfeld, Germany) laser diffraction particle sizer was used with the R2 lens (Range: 0.45–87.5 μm) to obtain the droplet size of selected samples.[14–16] The methodology was selected based on the fact that it could be used to detect differences in the volume size distribution (VSD) for a number of environmental and formulation parameters (unpublished data). Each sample was evaluated as a VSD of aerosol spray droplets using the Fraunhofer model in the Windox software program (Sympatec, GmbH, Clausthal-Zellerfeld, Germany). A special ''sprayer'' adapter supplied by Sympatec was used to perform automatic actuation of the MDI. The VSD profile was obtained at a spray distance of 18 cm to the laser beam (measured from the actuator mouthpiece). Based on the preliminary screening of the aerosol plume length, it was decided that aerosol droplets emitted at this distance would provide a good representation of the product. Also, beam steering,[14] which refers to the appearance of false peaks due to the vaporization of the spray in the beam's path, was not significant at this spray distance. The measurement begins after the first few spray droplets pass through the laser beam and stop when the spray decays below a detectable level. An approximation of the Fraunhofer model was used for assigning the diffraction angle and measured diffraction intensity to particle size and frequency, respectively. The VSD profiles are presented as a frequency distribution based on volume (log of density %). The experimental design involved sampling three individual sprays from each of the two inhalers tested.

In order to determine the impact of silicone on the droplet evaporation rate, the VSD of normal placebo samples were compared to those that were spiked with silicone. The placebo samples were prepared according

to Method II (two-stage manufacturing) except that the concentrate was added to the can immediately after compounding. The silicone-free valve was also employed. For the silicone-spiked samples, ≈400 μg silicone was added to the valve body, the plastic segment in contact with the product, before crimping the valve to the can. Prior to testing, these samples were agitated for several minutes.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) was performed using a Hitachi S-3500N (Hitachi High Technologies, Gaithersburg, MD). The aluminum sample stubs were mounted on a microscopy glass slide using double-sided sticky tape. Small circular double-sided conductive sticky tape was attached to the exposed side of the aluminum stub. The aerosol cans were primed twice by shaking the can for 5 seconds and firing to waste each time. The glass slide (with the sample stub mounted on it) was held 3–5 cm away from the MDI. The can was fired once to coat the sample stub with the spray. The stub was allowed to dry and then carefully removed from the glass slide. The stubs were then introduced into a sputter coater (Electron Microscopy Sciences, Fort Washington, PA) and coated with gold for 2 minutes. The samples were analyzed by SEM using the high vacuum mode at an accelerating voltage of 5 kV and magnifications of 1000X and 5000X.

RESULTS AND DISCUSSION

Physical Properties of Samples

In the visual inspection (qualitative only) of the product suspension properties filled into glass MDI containers, a more rapid flocculating suspension was noted when the high silicone valve was employed compared to that found with the low silicone valve. These observations suggest that silicone lubricant could enter the product and possibly even interact with the suspension. This was additionally corroborated by the fact that the spiking of silicone into the product also increased the rate of flocculation relative to the unspiked sample.

Particle Size by Cascade Impaction

The results obtained from this study have shown only a minor impact of valve on the total drug recovered from the cascade impactor stages and accessories, i.e., percent of label claim (Table 2). The largest effect was observed for the coarse drug substance batch in which a 10% difference between the sub-lots was found (Batch 2; Table 2). This difference, although not considered statistically significant ($p>0.05$, Table 2), may reflect the impact that silicone can also potentially have on drug content uniformity or micrograms of drug delivered per actuation.

On the other hand, the results show a much stronger impact of the valve silicone level on the distribution of drug on the cascade impactor stages (Tables 3 and 4). This is clearly illustrated in the % fine particles (FP), the fraction of the dose under 4.7 μm, which shows a significant reduction in value for the high-silicone valve sub-lot relative to the low-silicone and silicone-free valve sub-lots for all three batches ($p<0.005$, Table 4). Likewise, the MMAD, which is significantly larger for the high-silicone valve sub-lots relative to the others ($p<0.003$, Table 4), also exemplifies the effect that valve silicone level may have on the drug distribution in the impactor.

Table 3. Percent of drug in emitted dose on Andersen cascade impactor stages and accessories.[a]

			% Drug recovered from dose		
Batch	Sub-lot	Valve description	On impactor stages	On entry port	On casings
1[b]	A	Low silicone	83.8±1.5	12.5±1.9	3.69±0.42
	B	High silicone	80.6±4.4	15.4±3.9	5.47±0.43
2[c]	A	Low silicone	82.6±4.2	8.35±1.2	6.26±0.29
	B	High silicone	77.3±1.6	12.7±1.7	9.83±0.41
3[d]	A	Low silicone	76.1±5.1	18.1±5.2	5.78±0.99
	B	High silicone	63.2±13.0	28.9±14.9	7.93±2.13
	C	Silicone free	78.5±8.5	15.6±9.3	5.92±1.02

[a]Described in the experimental section, average and standard deviation values reported.
[b]N=six samples.
[c]N=three samples.
[d]N=two samples; each sample tested three times.

Table 4. Calculated values for % fine particles and MMAD.[a]

Batch	Sub-lot	Valve description	% Dose, as fine particles (<4.7 μm)	MMAD, μm	(GSD)
1[b]	A	Low silicone	75.1±1.2	2.45±0.01	(1.85±0.01)
	B	High silicone	65.3±3.6	2.88±0.01	(1.91±0.01)
	p-value	Sub-lots A*B	<0.001	<0.001	
2[c]	A	Low silicone	56.6±3.9	3.09±0.10	(2.25±0.01)
	B	High silicone	41.3±2.0	4.27±0.30	(2.33±0.11)
	p-value	Sub-lots A*B	0.004	0.003	
3[d]	A	Low silicone	41.5±2.2	3.85±0.15	(2.25±0.12)
	B	High silicone	29.9±4.3	4.43±0.29	(2.40±0.10)
	C	Silicone Free	46.5±3.9	3.56±0.12	(2.19±0.03)
	p-value	Sub-lots A*B	<0.001	0.001	
		Sub-lots A*C	0.022	0.005	
		Sub-lots B*C	<0.001	<0.001	

[a]Described in the experimental section, average and standard deviation values reported.
[b]N=six samples.
[c]N=three samples.
[d]N=two samples; each sample tested three times.

It appears from the % dose collected on the stages as well as the PSD profile of Batch 3 that the PSD of the silicone-free valve sub-lot may even be distinguished from that of the low-silicone valve (Tables 3 and 4, Fig. 1). The shift towards larger particle size with an increase in silicone is illustrated graphically on the PSD profiles (Fig. 1). The fraction under 4.7 μm, % fine particles, shows an inverse relationship with the amount of valve silicone (sub-lot C>A≫B; Table 4). The MMAD and GSD reflect, respectively, the direct relationship of particle size and broadness of distribution with the valve silicone level (Table 4). These results imply that even low levels of silicone in the valve could potentially impact the aerodynamic droplet size.

Particle Size by Laser Diffraction

As in the cascade impaction PSD profile (Fig. 1), the results by laser diffraction show distinctly different

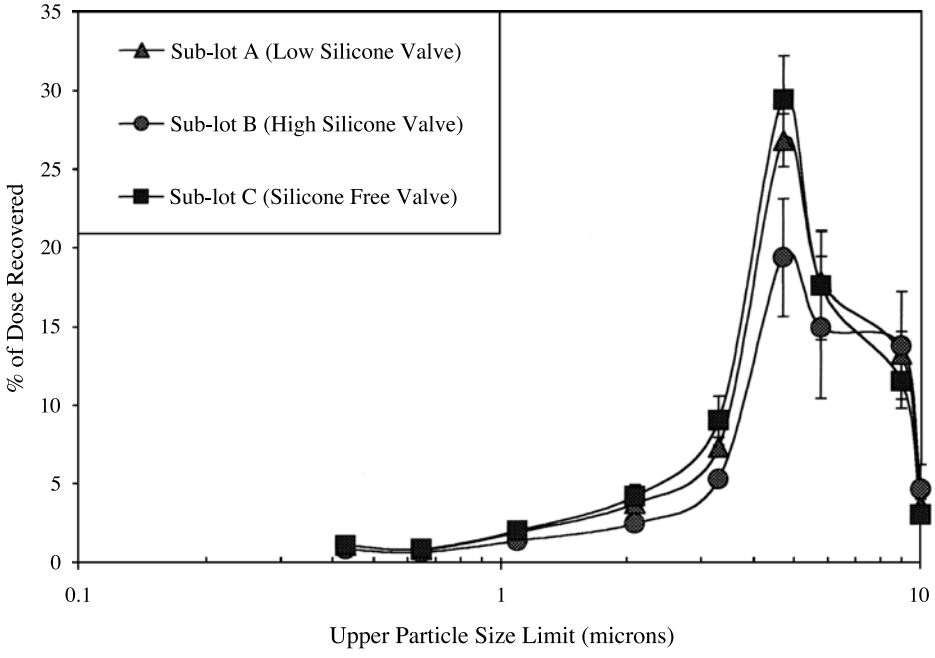

Figure 1. Particle size distributions obtained using Andersen cascade impaction for Batch 3 (mean and standard deviation).

VSD profiles for each of the valve sub-lots (Fig. 2, Batch 3). These results suggest that silicone may influence the droplet size of the emitted spray. However, the VSD trend, which shows a rank order decrease in droplet size with an increase in silicone, is opposite to that seen in cascade impaction, where the aerodynamic particle size increases as a function of silicone.

Upon completion of the droplet size testing of the placebo by Sympatec, it was shown that the droplet size profiles (VSD) were identical for the normal and spiked placebo samples (sub-lots P1 and P2, respectively in Fig. 3). Thus, these results (Fig. 3) show no evidence that silicone impacts the droplet size or the droplet evaporation rate.

The different trends obtained by the Sympatec method compared to cascade impaction may be related to the fact that the VSD profile (Fig. 1) can contain the distributions of both drug-free and drug-containing droplets, whereas the cascade impaction profile only represents the distribution of drug droplets. The 1.5-μm peak in the VSD profile (Fig. 1) is considered most representative of drug-free droplets, since it is less likely that the drug particles would be contained in droplets of this magnitude. The peak at 4.5 μm (Fig. 1) is thought to represent drug droplets and additionally drug-free droplets, since it is shown in placebo profiles that drug-free droplets fall within the range of ≈1–10 μm. It is shown in the VSD profile (Fig. 2) that as the level of silicone in the valve increases, there is a larger contribution of the 1.5-μm peak relative to that at 4.5 μm.

In a well-dispersed suspension it is presumed that a high proportion of spray droplets will contain micronized drug substance leading to a distribution that is centered around the 4.5-μm region. Conversely, in suspensions where drug aggregation is prevalent, it is thought that there would be fewer, more concentrated drug droplets and, at the same time, an increased proportion of fine drug-free droplets in the 1.5-μm region. Therefore, if silicone causes significant drug aggregation, then the trend towards smaller droplet size with an increase in silicone may be possible.

The fact that the VSD profile shows a trend of decreasing droplet size with increasing silicone levels is consistent with other studies. There has been related phenomenon reported in the literature based on a study using the quartz crystal micro-balance (QCM) impactor, which uses piezoelectric quartz crystals to determine the frequency of the particles (which then gets converted to mass) impacting on the QCM plates.[17] As in the laser diffraction method, the QCM measures the size distribution of the drug along with any nonvolatile excipient. Any size distribution from such an impaction method would involve drug-free and drug-associated droplets. A reduction in droplet size was obtained for formulations in which nonvolatile ingredients were added, suggesting that the

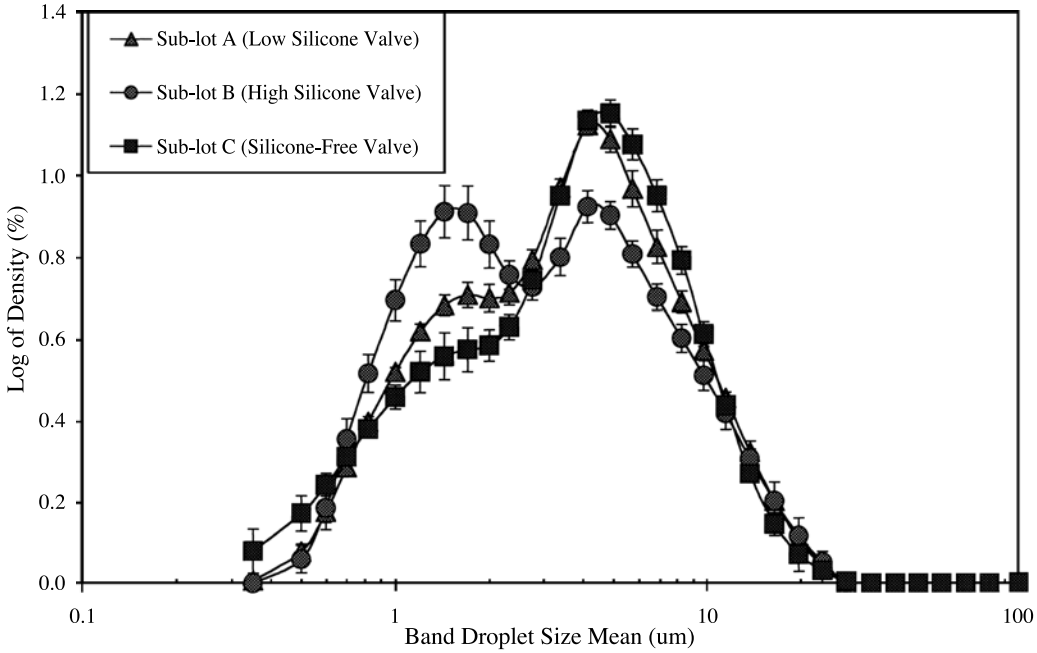

Figure 2. Frequency volume distributions obtained from laser diffraction for Batch 3 (mean and standard deviation).

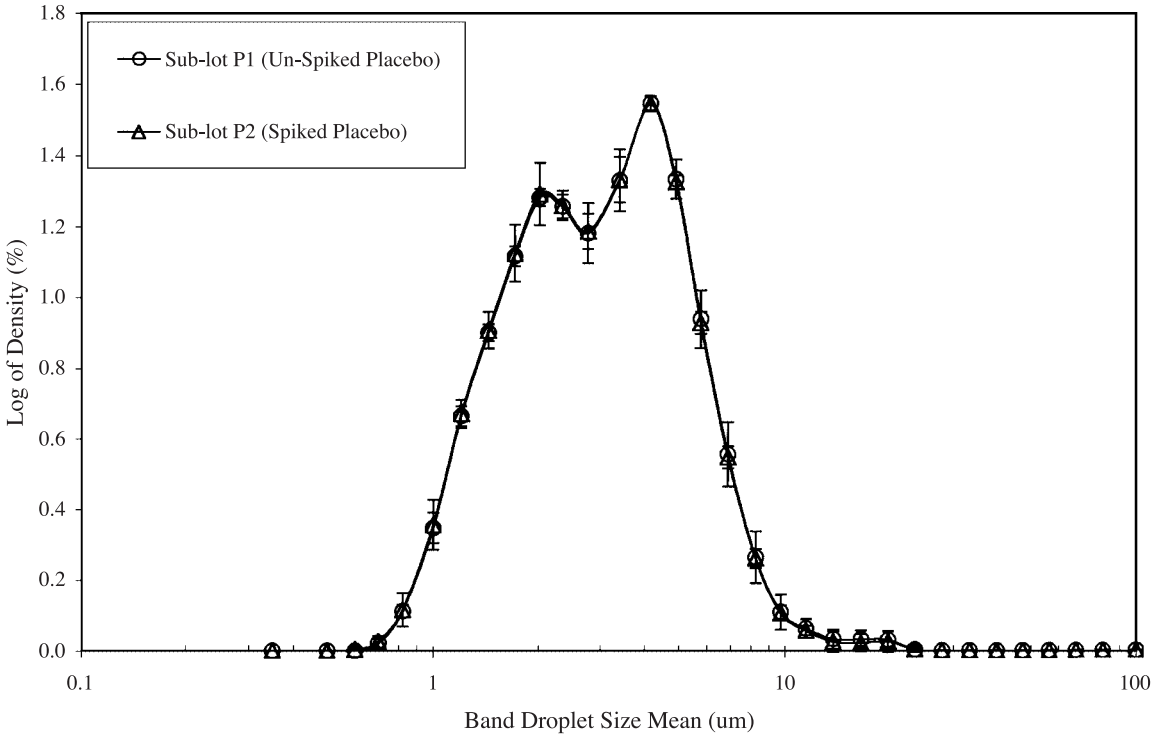

Figure 3. Frequency volume distributions obtained from laser diffraction for placebo MDIs (mean and standard deviation).

nonvolatile distribution was finer than that of the drug and caused the overall distribution to shift to a finer PSD.[17]

Similarly, in other work performed in this laboratory, a direct relationship was obtained between leachable level in the product contents and the aerodynamic particle size by cascade impaction of the emitted spray.[18] At the same time, an inverse relationship between droplet size by laser diffraction and leachable level was observed.[18]

Particle Size by Scanning Electron Microscopy

The SEM results show, qualitatively, that the primary particle size of the suspended drug in sub-lots A, B, and C are about the same at 1000X magnification (not shown) and 5000X magnification (Fig. 4). The primary drug particles for the three formulations ranged from 1–5 μm, and showed low axial ratios and rough edges, suggestive of well-micronized material. Despite the larger aerodynamic size obtained from cascade impaction with increasing levels of silicone (Fig. 1), evidence of a corresponding increase in primary drug particle size was not found (Fig. 4).

Proposed Mechanisms for the Interaction of Silicone with the Formulation

If silicone oil is in contact with the product contents, it is proposed that it could promote aggregation

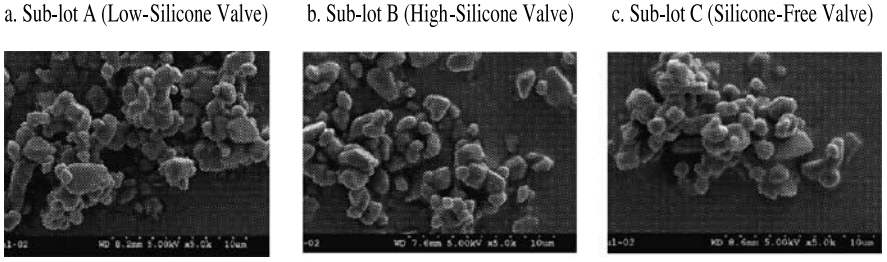

Figure 4. Scanning electron micrographs of plumes emitted from aerosol cans.

of the suspended drug particles. Silicone oil is insoluble in this suspension medium and may adhere to the surface of the drug particles modulating the aggregation kinetics of the suspended particles in such a way as to increase the aerodynamic particle size in the emitted aerosol plume.

It is plausible that the drug particles could be coated by silicone oil since both are of low polarity. The presence of surfactant in the formulation, a long chain fatty acid, may also aid in the stabilization of the silicone oil at the drug surface. The adhesion of silicone oil to the drug surface could reduce the polarity of the drug, thus making it less likely to interact with the highly electronegative propellant medium and lead to an increase in interparticle attraction and aggregation of the suspended drug.

Factors that affect the surface energy of the particles (i.e., by steric or charge stabilization), including the addition of additives such as surfactants, have been shown to control their aggregation behavior.[19–25] Generally, these additives lead to reduced particle interaction.[21,22] However, in some cases, they have actually been found to promote interparticle attraction.[23–25] Furthermore, for a study involving a suspension MDI, the larger aerodynamic size has been linked to the high degree of interparticle attraction in the formulation.[25]

It can also be hypothesized that silicone oil is altering the evaporation kinetics of drug-associated droplets as observed in other MDIs by increasing the levels of surfactants or other nonvolatile ingredients.[26–28] Based on the fact that silicone did not appear to affect the droplet evaporation rate when spiked into a placebo (Fig. 3), no evidence for the occurrence of this phenomenon can be seen in this study.

There also appears to be no strong evidence of crystal growth in the sub-lots containing the high silicone valves, another mechanism by which the aerodynamic PSD can increase. This is based on the fact that microscopic evaluation of the product did not reveal any inter-lot differences in the size or shape of the suspended drug for Batch 3 (Fig. 4).

CONCLUSION

In this work, evidence showing that high levels of silicone oil in the MDI valve can have an impact on aerodynamic PSD of the emitted aerosol is presented. Since it is critical that the aerodynamic PSD of MDIs be tightly controlled, it is important that all factors (i.e., formulation and packaging component related) should be carefully evaluated and their effect on final product quality well understood during product development.

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Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016