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RESEARCH ARTICLE

The application of "in-flight" laser diffraction to the particle size characterization of a model suspension metered dose inhaler

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Abstract

Laser diffraction (LD) has been used to measure the particle size of pharmaceutical aerosols. In this study, the application of LD for measuring the particle size of a model suspension metered dose inhaler (MDI) containing a hydrofluorocarbon propellant was investigated using a Sympatec LD apparatus with an automatic spray device. In order to obtain meaningful results, test parameters such as spray distance and temperature needed to be optimized for this model formulation and then well-controlled during testing. Using a suitable LD test methodology, it was found that particle size variations as a function of nonvolatile excipient levels as well as changes to the suspended drug substance could be observed and, in some cases, correlated to cascade impaction results. Based on these studies, it is believed that the methodology is a valuable rapid screening tool for investigating variations in or permutations to suspension MDI formulations. Nonetheless, the trends in the LD droplet size are complicated by the presence of drug-free droplets. Consequently, the results are not always consistent with other particle sizing techniques such as cascade impaction in which the droplets associated with drug are evaluated. Therefore, for suspension MDIs, the "in-flight" LD method would probably best be utilized as a complementary sizing technique during formulation development.

Keywords: Laser diffraction, Andersen cascade impaction, volume size distribution, pressurized metered dose inhaler (pMDI), suspension

Introduction

A pressurized metered dose inhaler (pMDI) is a propellant-based pharmaceutical aerosol widely used in the treatment of pulmonary diseases. The delivery efficiency of a pMDI to the respiratory tract and its physical stability are greatly affected by the particle size of aerosols upon actuation. Consequently, characterization of particle size becomes very critical in the assessment of product performance during formulation development. The particle sizing techniques of pMDI aerosols are categorized as aerodynamic measurements based on inertial separation principles and optical methods using microscopy or light scattering (Dolovich, 1991). Among these techniques, Andersen cascade impaction (ACI), the method specified for regulatory approval, is the most widely used although it is very time-consuming and labor-intensive. Alternatively, laser diffraction (LD) has been identified as a rapid and noninvasive method for real-time plume–particle size measurement of pMDI aerosols (Ranucci, 1992; Hallworth, 1993). In recent years, advances in the development of the LD technique have led to its increased use in the assessment of different classes of inhalation aerosols and a comprehensive review regarding its applications and limitations has been reported (Mitchell et al., 2006). The LD measurements for nebulizer solutions (Clark, 1995; Kwong et al., 2000; Vecellio None et al., 2001), aqueous aerosols (Ziegler and Wachtel, 2005), and dry powder inhalers (de Boer et al., 2002a,b; Marriott et al., 2006; Pilcer et al., 2008) are more straightforward since no propellant is present. Its application in pMDIs, however, is more challenging in that propellant evaporation unavoidably causes dynamic changes to the aerosol droplet size during the measurement. Therefore, test parameters including temperature, humidity, air flow rate, spray concentration, and spray distance to the lens must be optimized and well-controlled during the measurement to minimize the variability and the bias in the results.

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One of the limitations of the LD method is that it is incapable of providing chemically specific information for the drug substance in the aerosol. As a result, characterization of the particle size of a suspension pMDI becomes more complex than that of a solution pMDI due to the presence of both drug-containing and drug-free droplets in the aerosol cloud.

A solution pMDI consists of relatively homogeneous liquid spray droplets and, consequently, the LD method was shown to be an effective way to evaluate the impact of time and space on the pMDI spray dynamics (Smyth and Hickey, 2002a,b) as well as droplet size changes as a function of formulation changes, that is, co-solvent concentration (Smyth and Hickey, 2002a,b). The particle size obtained from LD was reported to be comparable or, at least, correlated to the ACI results (Holmes et al., 2001; Smyth and Hickey, 2003; Haynes et al., 2004).

For the LD measurement of suspension pMDIs, the primary particle size can be characterized by dispersing the aerosol suspension in a liquid cell (Feddah and Davies, 2004) or in a propellant-filled pressure cell (Jones et al., 2004, 2005). In contrast, the "in-flight" LD measurement allows one to capture the real-time droplet size distribution of a plume, which may provide more insight into the drug deposition pattern in the airway. During an "in-flight" LD measurement, the aerosol is sprayed directly into the path of a helium–neon laser beam. The light is diffracted from individual aerosol droplets to the photodiode detectors. Analysis of the detector output yields a volumetric size distribution (VSD) based on the Mie theory or Fraunhofer theory (Annapragada and Adjei, 1996).

Previous work has shown that the "in-flight" LD method can distinguish suspension pMDIs of varied formulation parameters such as raw active pharmaceutical ingredient (API) size (Sharpe et al., 2002), valve lubricant concentration (Berry et al., 2004a,b), and dose strength (Cooper and Bell, 2008). However, the impact of testing conditions and nonvolatile excipient on the measuring results have not been fully addressed, although it is known that the presence of nonvolatile excipients in a pMDI formulation could greatly affect the particle size distribution (PSD) of the aerosol (Simons and Stein, 2005). Some effort has been made to compare the "in-flight" LD results of a suspension pMDI with the impaction results, but no significant correlation has been obtained so far (Holzner and Mueller, 1995; Jones et al., 2005).

This study consisted a more extensive evaluation of the capability and reliability of the "in-flight" LD method for the measurement of suspension pMDI droplet size. Using a model suspension pMDI formulation, the sensitivity of the method to test parameters such as spray distance and temperature, as well as formulation parameters such as nonvolatile excipients and API size, was investigated. As part of this evaluation, the PSD data obtained from the LD method and the standard ACI method are compared.

In the following sections, the term LD method specifically refers to the "in-flight" measurement, unless stated otherwise.

Materials and methods

Active pharmaceutical ingredient

The API was manufactured using a jet-mill micronizer with varied feed rates. The median particle size of different lots of APIs ranged from 1.1 to 1.8 μm. The PSD profile of the API was characterized using LD (Sympatec HELOS Compact, model KA with a R2 helium–neon laser GmbH, Windox Software 3.0, Clausthal-Zellerfeld, Germany). The crystallinity of the API was confirmed by DSC (TI Model 2920, heating rate 10°C/min, Amorphous LOD ~1%).

pMDI manufacture

pMDI suspension samples were manufactured with a hydrofluorocarbon (HFA) propellant (Solkane, Solvay, UK). The formulation contained <0.2 wt% nonvolatile surfactant as well as <5 wt% alcohol as co-solvent. About 10 g of the formulation was filled into a commercially available aerosol can that was crimped with a typical 63-μL valve and tested with an actuator for oral delivery. All samples were stored at ambient room conditions for ~2 weeks after manufacture.

In order to evaluate the sensitivity of the LD method to the presence of nonvolatile ingredients in a suspension pMDI, food grade silicone oil, a typical valve lubricant, was spiked into the sample during product manufacturing and compared with the unspiked samples. The silicone oil level ranged from 0.5 to 10 mg per sample.

LD particle size analysis

The droplet size of a pMDI sample was measured by a Sympatec LD particle-sizer (HELOS Compact, Model KA; Sympatec GmBH, Clausthal-Zellerfeld, Germany) with the R2 lens (range: 0.45–87.5 μm). A special "Sprayer" adapter supplied by Sympatec was used to perform automatic actuation of the pMDI. The instrument setup was on an open bench with no enclosed air flow control during the time the study was conducted. In order to investigate the effect of the test temperature on the LD results, a series of test temperatures ranging from 15°C to 30°C were selected. For each condition, the test sample was primed once and then put in a temperature-controlled water bath for 5 min prior to the measurement. Subsequently, the canister was removed from the bath and dried, shaken vigorously for 5 sec, then quickly placed onto the sprayer attachment and actuated for the measurement. The VSD of aerosol spray droplets of each sample was evaluated using the Fraunhofer model in the Windox software program (Sympatec GmbH, Clausthal-Zellerfeld, Germany). The measurement started after the first few spray droplets passed through the laser beam and stopped when

the spray decayed below the detectable level. Three replicate pMDI samples were tested for each condition. Method development work to select the optimal trigger condition and the sprayer settings was conducted prior to this study and the identified test parameters are listed in Table 1.

ACI particle size analysis

The Andersen 1 ACFM Mark II Cascade Impactor apparatus was used with a 1-L glass entry port. The 1-L glass entry port was selected instead of the USP entry port because the former has been found to be better able to detect subtle changes in PSD in an HFA-based suspension pMDI (Naini et al., 2004). The air flow rate was set at 28.3 L/min. A total of two actuations of a pMDI canister were sprayed into the apparatus mouthpiece in each measurement. The cutoff size range was 0.43–10 μm. Three replicate pMDI samples were tested for each batch. Chemical analysis was performed using a validated assay on a Waters Integrated Millennium HPLC system (Waters, UK). All the tests were conducted in a controlled room at 21°C/30% RH. The fine particle fraction (FPF) was defined as the mass ratio of particles collected on stage 3 and above of the ACI apparatus, that is, the percent of particles <4.7 μm.

Results and discussion

Sensitivity of LD to the spray distance and temperature

The VSD of a pMDI sample was measured as a function of temperature at spray distances of 8 cm and 12 cm to the laser beam (measured from the actuator mouthpiece), respectively. If the actuator orifice is too close to the laser beam, large quantities of propellant evaporating in the beam's path will have a different refractive index than air and will erratically alter the path of the light diffracted by the particles, producing erroneous measurements. This phenomenon is known as beam steering (Ranucci, 1992). At the opposite extreme, when the actuator orifice is located too far away from the laser beam, the concentration of particles in the beam will be too low to produce sufficient diffracted light to the detector for reliable measurement (Dolovich, 1991). Based on the preliminary screening of the aerosol plume length, it was decided that aerosol droplets emitted at this spray distance range would provide a good representation of the product with minor beam steering. The results are shown in Figure 1A and B. With an increase of temperature, the VSD became narrower and the median particle size shifted to a lower value. At the same

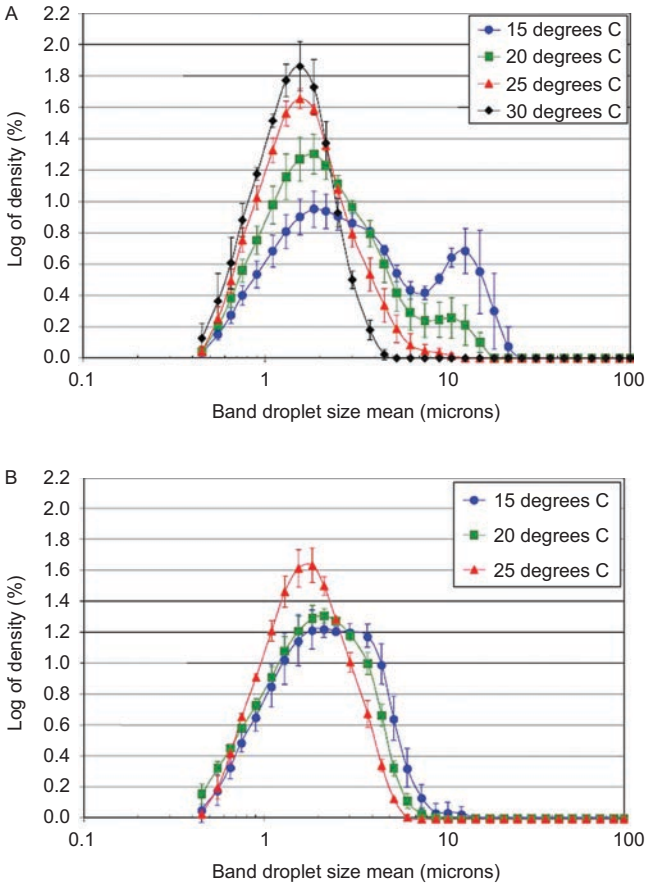

Figure 1. (A) Frequency volume distributions obtained from laser diffraction Sympatec volumetric size distribution (VSD) as a function of temperature at 8 cm spray distance for hydrofluorocarbon (HFA) propellant. (B) Frequency volume distributions obtained from laser diffraction Sympatec VSD as a function of temperature at 12 cm spray distance for HFA propellant.

Table 1. Summary table of testing parameters for laser diffraction measurement.

Product parameters		Trigger condition parameters		Sprayer setting parameters	
Density	1.40 g/cm^3	Duration	10 sec, single	Sledge position	170 mm
Shape factor	1.00	Time base	5 msec	Stroke	5 mm
Complex refractive index	2.67	Start series	0.00 sec after channel 21 ≥ 1.0%	Inclination angle	0
Forced stability	0 or 2*	Stop series	1.00 sec after channel 21 ≤ 0.9%	Trajectory recording	1.00 msec
Temperature	15°C, 20°C, 25°C, 30°C	Stop series alternative	After 5.00 sec real time	Stroke recording	ON
		Split series	Periods of 1.00 sec real time	Max trajectory velocity	125 mm/sec
				Trajectory acceleration	1.50 mm/sec^2
				Vacuum extraction delay	3 sec

*Forced stability equals 0 when not in use and 2 when eliminating last two detection channels.

temperature, the median particle size decreased with the increase of the spray distance from 8 cm to 12 cm. It implies that evaporation dynamics of aerosol droplets plays an important role in the "in-flight" LD measurement. Droplets evaporate faster at high temperatures and when traveling longer distances, leading to a narrower droplet size distribution and smaller median size value. Therefore, test conditions such as spray distance and temperature must be kept constant during the measurement to assure the comparability of the results. In the later measurements, the test temperature was kept at 25°C at all times, if not stated otherwise.

Sensitivity of LD to nonvolatile ingredients in a suspension pMDI

The particle sizes of the pMDI placebo and active samples, as well as the samples consisting of neat HFA propellant, were measured at a spray distance of 12 cm. As shown in Figure 2A, the pMDI samples of neat HFA propellant had a smaller median particle size and narrower VSD than the placebo and active samples, although the VSD of the placebo and the active samples were not distinguishable from each other. It suggests that aerosol droplets are increased by the presence of nonvolatile surfactants and co-solvents due to the reduced evaporation rate. The distinction between the placebo and the

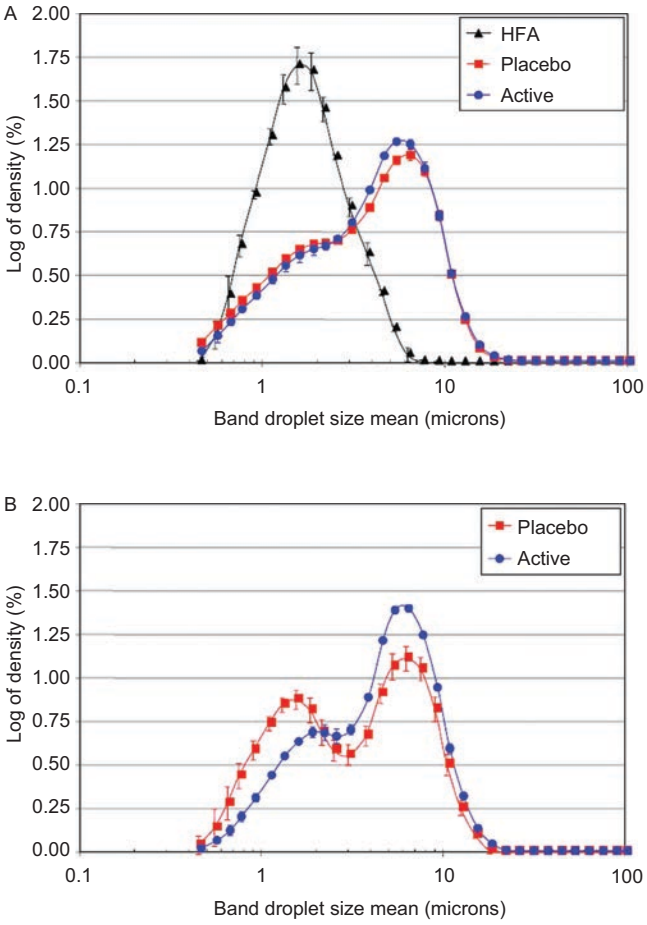

Figure 2. (A) Frequency volume distributions obtained from laser diffraction Sympatec volumetric size distribution (VSD) as a function of formulation at 25°C and 12 cm spray distance. (B) Frequency volume distributions obtained from laser diffraction Sympatec VSD as a function of formulation at 25°C and 18 cm spray distance.

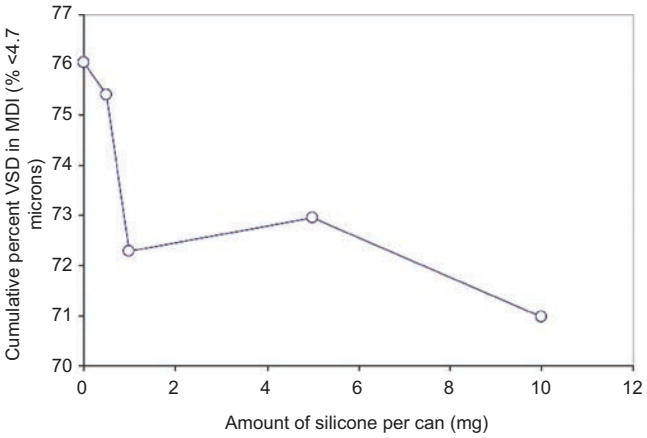

Figure 3. Cumulative percent of droplet size below 4.7 μm as a function of spiked silicone level.

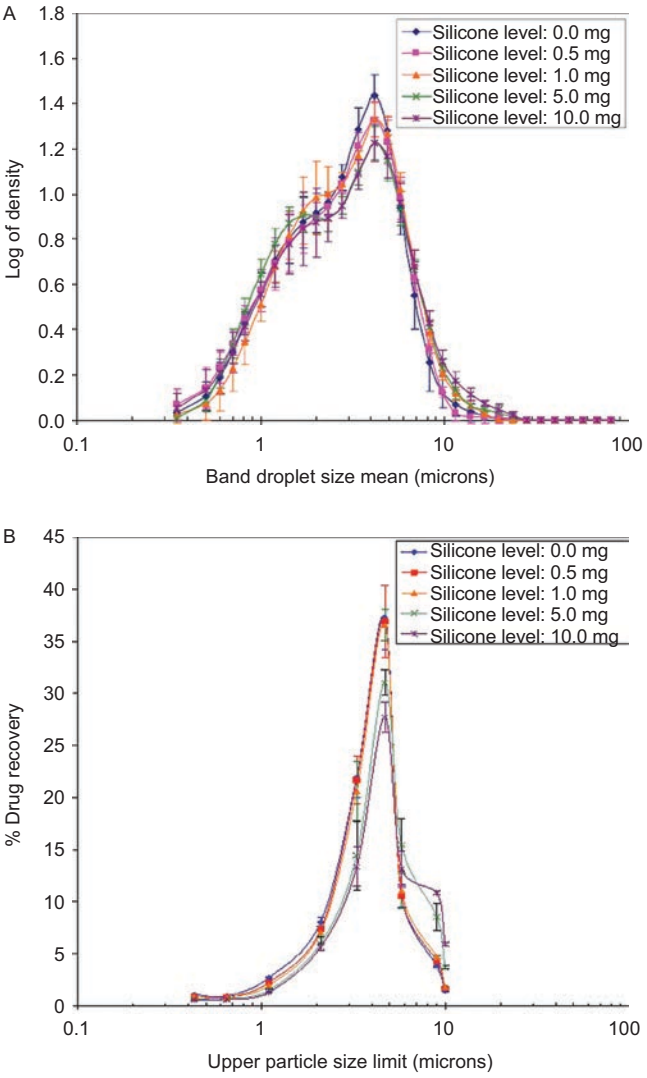

Figure 4. (A) Droplet size distribution as a function of spiked silicone level obtained from laser diffraction. (B) Particle size distribution as a function of spiked silicone level obtained from cascade impaction.

active formulations became more pronounced as the measuring zone distance increased from 12 cm to 18 cm, as shown in Figure 2B. Therefore, the test distance was kept at 18 cm for the later measurements. Both the active and the placebo formulations exhibited a bimodal PSD. The active formulation produced a slightly coarser PSD than the placebo. It suggests that the presence of fine API particles also had some effect on aerosol droplet size, although it was not as significant as those of the excipients. When the spray distance is optimized to capture the changes in the dynamic evaporation rate of droplets caused by presence of nonvolatile components, the method can be used to differentiate neat HFA propellant, placebo, and active pMDI formulations at appropriate test conditions.

As shown in Figure 3, with increasing spiked silicone level in the pMDI formulation, the cumulative percent of fine droplets below 4.7 μm was reduced. The reduction was greater at lower silicone levels. This trend was consistent with previous findings in which pMDI samples with valves containing high silicone levels produced a larger aerodynamic particle size by cascade impaction than samples with low silicone valves (Berry et al., 2004a,b). It is speculated that silicone oil could promote aggregation of the suspended drug particles by changing the interparticle interaction energies (Berry et al., 2004a,b) and/or alter the evaporation kinetics of aerosol droplets by increasing the levels of nonvolatile ingredients (Brambilla et al., 1999). In either mechanism, its impact on fine droplet populations was able to be captured by the LD method. Nonetheless, the change in the VSD profiles and the median droplet size (D_{v50}) as a function of silicone level was less pronounced with the LD method than with the ACI method, in part due to the relatively large data variability of the LD result, as shown in Figure 4 and Table 2. An enclosed system may be utilized in the LD measurements in future studies to minimize the variations caused by droplet evaporation.

Sensitivity of LD to API size in a suspension pMDI

In order to evaluate the impact of the particle size of the API on the VSD of the pMDI active samples, six lots of pMDI suspensions were manufactured with APIs of varied median particle size from 1.14 to 1.77 μm. Figure 5A and B give the size distributions of the drug substance lots and their corresponding pMDI products, respectively. Although the drug substances had only one mode in their size distribution, all six pMDI batches display a similar bimodal droplet size distribution profile with maxima at ~1.7 and 5 μm. The second peak of the VSD profile became shorter and broader as the API median size increased, whereas the first peak was not distinguishable between different formulations. In addition, the fine droplet fraction, defined as the cumulative percent of droplet size <4.7 μm, decreased with the increase of the API median size, as shown in Figure 5C. This suggests that pMDI products with larger drug substance medians tend to have wider and coarser droplet size distributions. This trend is consistent with what has been observed by ACI measurements (Berry et al., 2004a,b). Sharpe et al. (2002) found that the LD technique was capable of distinguishing the pMDI formulations with an API median size of above 2.3-fold difference but did not capture the pMDI droplet size difference when the API median size was <1.5-fold different. Given the relatively smaller size differences between the six API lots, this study was approaching the sensitivity limit of the LD.

Table 2. Cascade impaction and laser diffraction measurements of pressurized metered dose inhaler (pMDI) samples with varied silicone levels.

	Cascade impaction		Laser diffraction	
Silicone level (mg/can)	MMAD (μm)	FPF (%) (below 4.7 μm)	D_{v50} (μm)	Cumulative percent below 4.70 μm (%)
0	2.72 (0.05)	71.9 (0.6)	2.85 (0.17)	75.2 (3.8)
0.5	2.82 (0.03)	69.8 (1.9)	2.88 (0.19)	74.0 (2.6)
1	2.89 (0.08)	67.8 (2.2)	2.96 (0.13)	72.3 (1.8)
5	3.48 (0.18)	54.2 (4.0)	2.81 (0.19)	72.7 (2.3)
10	3.84 (0.08)	49.1 (1.8)	2.98 (0.23)	70.5 (3.3)

Table 3. Cascade impaction and laser diffraction measurements of pressurized metered dose inhaler (pMDI) samples with varied active pharmaceutical ingredient (API) sizes.

	Cascade impaction		Laser diffraction	
API median size (μm)	MMAD μm)	FPF (%) (below 4.7 μm)	D_{v50} (μm)	Cumulative percent below 4.70 μm (%)
1.14	2.58 (0.05)	79.0 (2.0)	3.78 (0.09)	70.4 (2.9)
1.19	2.63 (0.06)	76.0 (4.0)	3.51 (0.05)	71.9 (1.5)
1.25	2.83 (0.05)	68.0 (1.0)	3.61 (0.04)	68.5 (1.3)
1.38	3.09 (0.10)	58.0 (1.0)	3.34 (0.05)	69.8 (1.2)
1.53	3.54 (0.16)	50.0 (3.0)	3.64 (0.03)	67.9 (2.7)
1.77	4.38 (0.20)	38.0 (2.0)	3.61 (0.04)	65.9 (1.5)

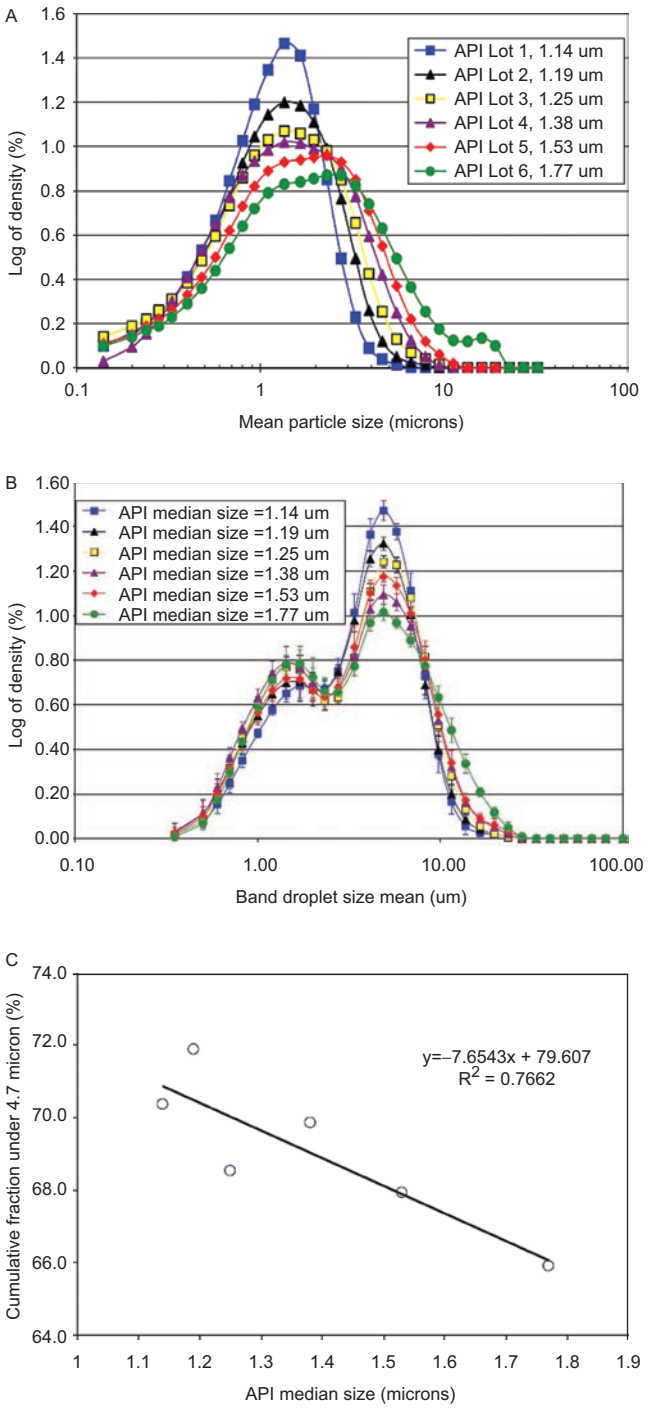

Figure 5. (A) Active pharmaceutical ingredient (API) particle size distribution measured by Sympatec laser diffraction. (B) Droplet size distribution of pressurized metered dose inhaler (pMDI) products measured by Sympatec laser diffraction. (C) Cumulative percent of droplet size below 4.7 μm as a function of API median size.

As a result, the VSD difference was attenuated as the API size difference decreased. However, a difference in fine droplet fraction was shown between the six lots despite the small API size difference. Hence, the LD method is capable of distinguishing suspension pMDIs with different API size, but the sensitivity may depend on the formulation and the API particle size ranges.

Comparison between LD and cascade impaction

It is known that the LD method measures VSDs based on the surface properties of droplets, whereas cascade impaction measures the aerodynamic size distribution based on the mass of drug particles. This difference in fundamental measuring principles makes the direct comparison between the two methods challenging.

In this study, pMDI samples with different API size and spiked silicone level as described in the last two sections were also measured using the cascade impaction method. For the six pMDI batches with different API median sizes, the median droplet size (D_{v50}) and the cumulative percent of droplets below 4.7 μm, which were characterized by the LD method, are compared with the mass median aerodynamic diameter (MMAD) and the FPF measured by the cascade impaction method (Table 3). The same comparison was conducted for the five pMDI batches with different spiked silicone levels. The size distribution results from both methods are shown in Figure 4A and B, and Table 2. It can be seen from Figure 4 that cascade impaction provided a narrow unimodal distribution with a peak value at around 5 μm, whereas LD provided a wide bimodal distribution with two peaks at 1.5 and 5 μm. As stated earlier, the LD measurements are affected by the evaporation rate of the aerosol droplets, and the results are often complicated by the presence of drug-free droplets. As a consequence, the aerosol size may be underestimated or overestimated. As seen in Tables 2 and 3, the absolute values of MMAD and FPF from cascade impaction are comparable with the LD measurements for the lower ends of silicone levels and API sizes, although the discrepancies between the two methods increased as the silicone levels and API sizes increased. The change in particle size as a function of API size or silicone level are more apparent in cascade impaction than in LD, although the repeatability of the two methods was comparable as shown by their similar standard deviations. This implies that cascade impaction is a more sensitive method for detecting effects of formulation changes, particularly subtle changes, on the PSD of pMDI products.

Conclusions

This study showed that the "in-flight" LD method is a vital and rapid means to characterize the real-time droplet size distribution of a pMDI suspension product. Suitable settings for test parameters such as temperature and spray distance to the detector had to be established and well-controlled during testing in order to obtain meaningful results. Using the appropriate LD methodology, changes in the pMDI formulation composition were then detected. The droplet size distribution became broader relative to neat propellant when the model formulation contained other materials such as co-solvent, surfactant, valve lubricant, or API. The median droplet size increased and the FPF was reduced with larger API median sizes or

higher levels of nonvolatile ingredients. Moreover, these results showed trends that were comparable with those from corresponding cascade impaction measurements. Since LD results are not always consistent with cascade impaction results due to the complication of drug-free droplets and evaporation of propellant, the sensitivity of the method may be limited depending on the variations in formulation parameters. Therefore, to get a reliable result, it is critical that optimal test conditions be established based on formulation characteristics and testing conducted in a well-controlled environment. Despite a variety of challenges with complex formulations, the LD technique can be a valuable particle sizing tool for rapid formulation screening of suspension pMDIs.

Declaration of interest

The authors report no declarations of interest.

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