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Evaluation of metered dose inhaler spray velocities using Phase Doppler Anemometry (PDA)☆

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ABSTRACT

Droplet velocity is an important parameter which can significantly influence inhalation drug delivery performance. Together with the droplet size, this parameter determines the efficiency of the deposition of MDI products at different sites within the lungs. In this study, Phase Doppler Anemometry (PDA) was used to investigate the instantaneous droplet velocity emitted from MDIs as well as the corresponding droplet size distribution. The nine commercial MDI products surveyed showed significantly different droplet velocities, indicating that droplet velocity could be used as a discriminating parameter for in vitro testing of MDI products. The droplet velocity for all tested MDI products decreased when the testing distance was increased from 3 cm to 6 cm from the front of mouthpiece, with CFC formulations showing a larger decrease than HFA formulations. The mean droplet diameters of the nine MDIs were also significantly different from one-another. Droplet size measurements made using PDA (a number-based technique) could not be directly compared to results obtained using laser light scattering measurements (a volume-based technique). This work demonstrates that PDA can provide unique information useful for characterizing MDI aerosol plumes and evaluating MDI drug delivery efficiency. PDA could also aid the evaluation of in vitro equivalence in support of formulation or manufacturing changes and in evaluation of abbreviated new drug applications (ANDAs) for MDIs.

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1. Introduction

Metered-dose inhalers (MDIs) have grown in popularity since their introduction in the late 1950s, and they are currently used by millions of patients worldwide for the treatment of a variety of diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and other lung diseases characterized by obstruction of airflow and shortness of breath.

As a result of the Montreal Protocol on Substances that Deplete the Ozone Layer, chlorofluorocarbon (CFC) based inhalers are being replaced by hydrofluoroalkane (HFA) propelled inhalers. Due to essential use considerations for medical aerosols, this process is being accomplished in phases over several years with several CFC-based medical aerosol products already removed from the marketplace.

Although the HFA propelled replacement products are said to have similar in vitro performance as the corresponding CFC propelled product, they have different patient use instructions and, in real-world use, they may have a different "feel" to the patient. Some patients report the new HFA product feels "softer", tastes different, has a different feel in the back of the throat or is a different temperature than their previous CFC product.

MDIs are designed to deliver aerosolized medication to the lungs, however their drug delivery efficiency is low. About 80% of the drug emitted from a MDI deposits in the oropharynx with only about 10–20% of the emitted dose making it to the lungs (Newman et al., 1981; Newman, 1985). Common problems leading to this low efficiency are high oropharyngeal deposition and difficulty in coordinating actuation with inspiration (Crompton, 1982).

The drug particles emitted from a suspension MDI can have aerodynamic diameters that are larger than the API particles because the API particles are coated with propellant or/and surfactant as they emerge from the actuator (Clarke and Newman, 1981). Emission of these large, high velocity particles leads to increased oropharyngeal deposition and, consequently, low drug delivery efficiency.

Of the two critical parameters that influence the MDI drug delivery, the droplet size has been well studied and may be measured using various techniques such as cascade impactor, laser light scattering, aerodynamic particle sizer (APS), and other imaging methods. The other critical factor, droplet velocity, although directly related to patient "feel" has largely been overlooked. To our knowledge, there have been only few papers published where

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spray/droplet velocity measurements have been made for MDI spray plumes.

High-speed photography was used to measure spray velocity by Dhand et al. (1988) and Hochrainer et al. (2005). Based on the assumption that the velocity of the leading edge of the aerosol cloud is a good first-order approximation of the aerosol velocity, high-speed photography may be used to estimate spray velocities by analyzing video frames of the leading edge of the aerosol clouds.

Crosland et al. (2009) used particle image velocimetry (PIV) to perform spatial resolved velocity measurements. PIV is a laser-based optical technique whereby two images are taken of particles illuminated by a laser sheet. For this technique, statistical cross-correlation was performed on discrete regions known as interrogation windows enabling detailed, spatially resolved velocity measurements to be obtained for the spray.

Dunbar et al. (1997) and Kakade et al. (2007) used Phase Doppler Anemometry (PDA) to characterize droplet velocity for MDIs, and recently this technique has been used by our research group to characterize nasal sprays (Liu et al., 2010). As a single point optical measuring technique, PDA allows simultaneous and non-intrusive measurement of the droplet size and velocity in real-time (Albrecht et al., 2003). By analyzing the Doppler-equivalent frequency of the laser light scattered by droplets, their velocity can be determined. Droplet size is determined by measuring the phase difference between two Doppler bursts detected by two detectors at different angular positions.

In this study, PDA was used to analyze both commercially available HFA and CFC MDI products. This is the first time that the velocities of HFA MDI formulations (including drug, surfactant or excipients) were analyzed. The velocity and droplet size of the HFA and CFC MDI products were compared.

2. Methods

Nine commercial MDI drug products were used as test products in this study. Three of them are CFC based suspensions. Five of them are HFA based suspensions, and one is HFA based solution. The detailed product information is given in Table 1.

A 1-D PDA System (Dantec Dynamics, Skovlunde, Denmark) with FlowLite transmitting optics (f = 160 mm) and FiberPDA receiving probes (f = 160 mm) was used to measure droplet velocity and size in MDI plumes at distances of 3 and 6 cm from the MDI mouthpiece. The BSA P60 Flow and Particle Processor of the PDA system were controlled by BSA Flow Software Version 4 to monitor the PDA system during the measurements.

A SprayVIEW MDx automated actuator (Proveris Scientific Corporation, Marlborough, MA), controlled by Proveris Viota software (Version 5.2.1) was used to control the MDI actuations. Each MDI product was auto-characterized with 0.3 kg force of contact and 6 kg force at the end of stroke. Actuation profiles for all MDI samples were symmetric with 50 mm/s actuation velocity, 3000 mm/s^2 actuation acceleration, and 100 ms hold time.

The experimental setup for MDI droplet velocity measurements is shown in Fig. 1. Ten MDI actuations were employed in each PDA measurement, with a 5 s hold time between each actuation. The PDA instrument was set to collect data for 60 s or count 10,000 particles whichever occurs sooner. Three repeated measurements were performed for each sample.

A Sympatec HELOS laser light scattering (LLS) system was used to measure droplet size distribution.

A Stable Micro Systems TA-XT.plus Texture Analyzer equipped with 750 g load cell was used to measure the impaction force at 6 cm from the front of the MDI mouthpiece.

3. Results and discussion

3.1. Droplet velocity

Since droplet velocities are higher and more consistent near the center of a spray plume (Dunbar et al., 1997; Liu et al., 2010), the average droplet velocity at the center of the spray plume was used as the metric for MDI characterization. To investigate sampling distance effects, the droplet velocity and size were measured at the distances of 3 cm and 6 cm from the front of the MDI mouthpiece, with the measurement zone positioned along the centerline of the MDI mouthpiece/orifice.

The PDA droplet velocity measurement results for the nine MDI products are listed in Table 1. Data represent results from 3 repeated measurements for each MDI product. For the nine MDI products, the mean droplet velocities ranged from 5.4 to 20.1 m/s and 4.7 to 11.7 m/s, at 3 and 6 cm distance from the front of mouth pieces, respectively. Among the tested products, Qvar had the lowest velocity at both distances, Flovent 44mcg and Flovent 220mcg had the highest velocity at the 3 cm and 6 cm distance respectively.

Application of the T-test showed statistically significant differences (at the 95% confidence level) in droplet velocity between most of the tested MDI products (except Albuterol and Flovent 44mcg at 6 cm distance).

In the early study by Dunbar et al. (1997), a relatively small difference in mean droplet velocity was observed for the HFA propellant vs. the CFC propellant. It was also observed that the CFC-based formulation containing drug and surfactant yielded a higher velocity than the propellant alone. In the present study, the survey result suggests that the droplet velocity from CFC MDIs is not necessarily higher than those from the HFA formulated products. Mixed results were observed for the velocities of the nine tested HFA and CFC MDI products with both HFA and CFC formulations delivering high and low droplet velocities. It appears that the change of propellant from CFC to HFA is not a determining factor of MDI droplet velocity. Rather droplet velocity of the MDI plume is determined by the product design with respect to valve and orifice.

Sampling distance effects on droplet velocity were investigated at 3 cm and 6 cm from the front of the MDI mouthpiece. A decrease in velocity was observed for all tested MDI products when the testing distance was increased from 3 cm to 6 cm from the front of mouthpiece. The velocity decrease varied widely among different MDI products, ranging from 3.7% for Proventil up to 45.0% for Flovent 44mcg.

Theoretically, CFC formulations could have a larger velocity decrease due to the faster evaporation rate of CFC propellants, which would decrease the kinetic energy quickly and thus reduce the droplet velocity faster along the spray distance. This might be useful in development for a single MDI product, but not for comparison of different MDIs. Our results showed that the Flovent 44mcg HFA had the largest velocity decrease among the surveyed samples. Flovent HFA 220mcg and ProAir HFA also showed large velocity decreases, comparable to those observed for the three CFC products.

For a complex product such as an MDI, many factors, such as design of the delivery device, geometry of the orifice, formulation type (suspension or solution), and presence of co-solvent or excipients, will influence its in vitro performance. The physical property differences between CFC and HFA propellant alone cannot guarantee that an HFA MDI will produce a “softer” plume than a CFC product.

3.2. Droplet size

PDA is an extension of Laser Doppler anemometry (LDA) and can determine not only the Doppler frequency shift of light refracted by a droplet within the flow (yielding velocity information) but

Table 1
Mean droplet velocity measured at the center of the plumes for nine commercial MDI products. Measurements were taken at 3 cm and 6 cm from the front of mouthpiece (unit: m/s. Values in the parentheses are standard deviations, $n = 3$).

MDI products	Formulation type	API(s)	Excipient	@ 3 cm	@ 6 cm	Decrease (%)
Albuterol	CFC suspension	Albuterol	Oleic acid	15.1 (1.6)	10.8 (0.5)	28.5
Combivent	CFC suspension	Ipratropium Bromide; Albuterol Sulfate	Soya lecithin	8.0 (0.3)	5.9 (0.3)	26.3
Maxair AutoHaler	CFC suspension	Pirbuterol Acetate	Sorbitan trioleate	9.6 (0.2)	8.0 (0.3)	16.7
Flovent HFA 220mcg	HFA suspension	Fluticasone Propionate	None	16.3 (1.7)	11.7 (0.2)	28.1
Flovent HFA 44mcg	HFA suspension	Fluticasone Propionate	None	20.1 (0.2)	11.0 (0.2)	45.0
ProAir HFA	HFA suspension	Albuterol Sulfate	Ethanol	8.9 (0.3)	6.7 (0.1)	24.5
Proventil HFA	HFA suspension	Albuterol Sulfate	Ethanol, oleic acid	6.5 (0.2)	6.3 (0.1)	3.7
Qvar (BDP HFA)	HFA solution	Beclomethasone Dipropionate	Ethanol	5.4 (0.1)	4.7 (0.2)	11.9
Ventolin HFA	HFA suspension	Albuterol	None	10.3 (0.1)	9.4 (0.2)	8.0

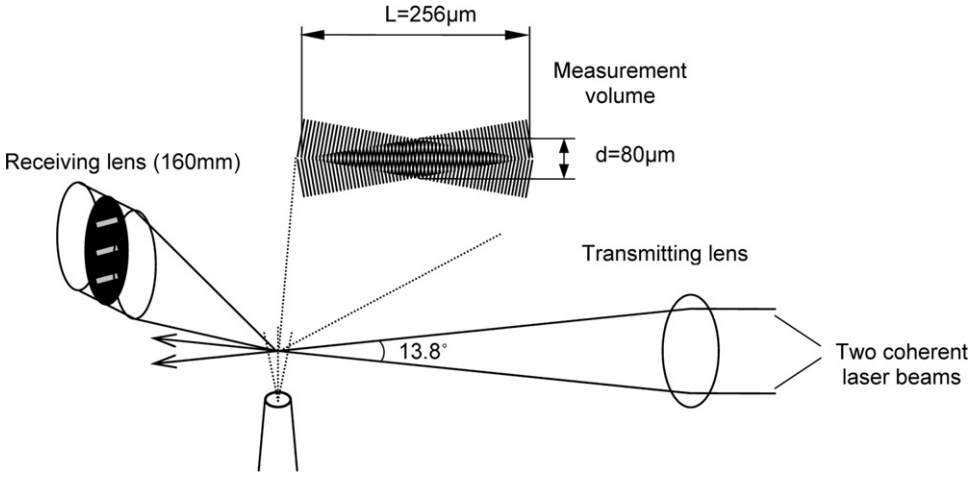

Fig. 1. Schematic of PDA system.

the phase shift can also be utilized to derive the diameter of the scattering droplets. The droplet size for the products tested in this study, reported as the arithmetic mean diameter (D10), are listed in Table 2. The volume mean diameter (D30) and volume median diameter (Dv50), calculated from the arithmetic mean diameter, are also provided in Table 2.

The droplet size of the nine MDI products were also measured by LLS under the same condition, and the LLS results (Dv50) are presented in Table 2 for comparison.

Droplet sizes (D10, D30 and Dv50) for all nine MDIs are statistically different from each other (except the pair of Flovent formulations). The droplet size parameters measured by both PDA and LLS were smaller at 6 cm than those measured at 3 cm. This may be due to the evaporation of the propellant in the MDI formulations.

The earlier study from Dunbar et al. (1997) showed that a HFA propellant produced smaller mean droplet size than did a CFC propellant. However, the particle size results of the nine commercial products showed mixed results when comparing HFA and CFC MDI products. As with droplet velocity discussed above, droplet size appears to be influenced more by valve and orifice design than by propellant.

When PDA and LLS droplet size measurements were directly compared for the same MDI products, D10, D30, Dv50 measured by PDA, and Dv50 measured by LLS were significantly different from each other ($p < 0.05$). This difference in the droplet size probably arises from fundamental differences in the measurement technique used.

PDA is a number based technique which measures individual droplets and provides number-weighted droplet size distribution, while LLS provides volume-weighted droplet size distribution.

In addition, the PDA and LLS instruments have much different measurement volumes. For PDA, the measurement zone is the

Table 2
Droplet size measurement results for the nine commercial MDI products by PDA (D10: arithmetic mean diameter; D30: volume mean diameter; Dv50: volume median diameter) and LLS (Dv50). Measurements were taken at the plume center for nine commercial products along the centerline of the MDI mouthpiece/orifice at 3 cm and 6 cm (unit: μm. Values in the parentheses are standard deviations, $n = 3$).

Product name	3 cm				6 cm			
	PDA			LLS	PDA			LLS
	D10	D30	Dv50	Dv50	D10	D30	Dv50	Dv50
Albuterol (CFC)	4.1 (0.3)	7.7 (0.3)	15.6 (0.2)	11.0 (0.9)	3.0 (0.3)	6.6 (0.5)	17.2 (0.7)	12.3 (1.0)
Combivent (CFC)	3.1 (0.0)	5.3 (0.3)	9.3 (0.5)	8.7 (0.6)	2.9 (0.1)	4.9 (0.1)	10.4 (0.5)	8.7 (1.0)
Maxair (CFC)	2.8 (0.1)	5.4 (0.1)	12.7 (0.2)	4.1 (0.6)	2.3 (0.1)	5.0 (0.3)	20.1 (3.8)	3.3 (0.1)
Flovent HFA 220mcg	3.2 (0.4)	6.1 (0.1)	13.2 (1.0)	3.9 (0.2)	2.2 (0.1)	5.5 (0.2)	19.0 (2.4)	3.8 (0.1)
Flovent HFA 44mcg	3.2 (0.4)	5.9 (0.2)	11.7 (0.0)	2.4 (0.1)	2.2 (0.1)	5.0 (0.3)	16.0 (1.0)	1.7 (0.2)
ProAir HFA	2.9 (0.1)	4.8 (0.2)	9.5 (0.5)	5.2 (0.4)	2.6 (0.1)	4.4 (0.2)	9.1 (0.7)	5.4 (0.4)
Proventil HFA	2.8 (0.1)	4.8 (0.1)	9.9 (0.2)	4.2 (0.1)	2.7 (0.0)	4.6 (0.3)	10.1 (1.2)	4.0 (0.5)
Qvar (BDP HFA)	2.3 (0.1)	4.0 (0.2)	9.2 (0.7)	2.9 (0.1)	2.0 (0.1)	3.5 (0.1)	9.1 (0.8)	2.6 (0.2)
Ventolin HFA	4.0 (0.3)	7.9 (0.4)	16.8 (0.6)	9.1 (0.5)	3.1 (0.2)	7.1 (0.4)	16.8 (0.5)	9.3 (0.2)

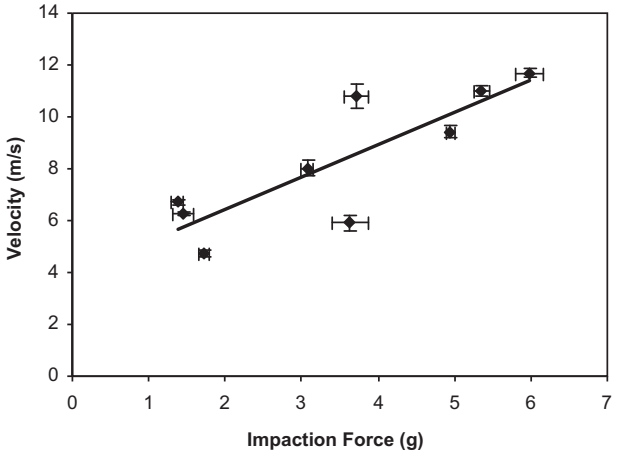

Fig. 2. Plot of impaction force vs. droplet velocity for the 9 tested MDI products. Data were measured at 6 cm spray distance from the front of mouth piece. The error bars in the plot show the standard deviations from three repeated measurements.

crossing point of the two laser beams, with a small measuring volume of 80 μm diameter; while for the LLS, the 18 mm diameter laser beam typically samples most of the MDI plume. Because the PDA samples only a small portion of the plume, measurement results are subject to local variability within that plume.

PDA will also be biased in favor of the larger droplets. At a given spatial coordinate, large droplets will scatter a large amount of light from the measurement volume, but for very small droplets, there may be insufficient scatter to produce a valid signal. The laser light scattering technique is an ensemble method for which the resulting signal arises from the diffraction pattern for a large number of droplets. The PDA technique, which analyzes diffraction from individual droplets passing through the measuring zone, is more subject to a bias toward larger droplets.

3.3. Droplet velocity vs. plume impaction force

From classical mechanics, impaction force and velocity are expected to be closely related. When an object of mass m moves with velocity v toward a stationary obstacle, there will be a time-dependent force F exerted on the object at the time of collision. The collision can be described quantitatively by the impulse-momentum theorem, which shows a direct relationship between force and velocity. The force exerted on the object and the impaction force exerted on the contact surface are a pair of action and reaction forces (Newton's third law of motion). They have equal values but opposite directions.

The application of the impulse-momentum theorem on MDI spray plume can be estimated by directly correlating impaction force with droplet velocity under the assumption that the aerosol mass at the time of collision is similar for the nine tested samples. Fig. 2 shows the impaction force vs. droplet velocity plot for the nine commercial MDIs at 6 cm spray distance from the MDI mouth piece. Both the impaction force and droplet velocity values shown in Table 3 represent averages from three repeated measurements. The results show that an MDI with higher droplet velocity tends to have a larger impaction force, as expected by the impulse-momentum theorem.

For an accurate correlation between the impaction force and droplet velocity, the aerosol mass at collision has to be taken into consideration. The aerosol mass at collision is related to the volume released for each actuation and spray pattern of the plume, which can be easily obtained for each product. However, due to different API concentrations and different propellant evaporated rates influenced by co-solvents and excipients from various formulations, the measurement of the aerosol mass at collision is much more complicated than it appears to, and beyond our capacity to do a thorough investigation at this time. Therefore, an accurate calculation of the relationship between droplet velocity and impaction force will not be further discussed in this paper.

Table 3
Comparison of average droplet velocity and impaction force at a distance of 6 cm from the MDI mouthpiece for nine commercial MDI products (values in the parentheses are standard deviations, $n = 3$).

MDI products	Impaction force (g)	Velocity (m/s)
Albuterol (CFC)	3.7 (0.2)	10.8 (0.5)
Combivent (CFC)	3.6 (0.2)	5.9 (0.3)
Maxair (CFC)	3.1 (0.1)	8.0 (0.3)
Flovent HFA 220mcg	6.0 (0.2)	11.7 (0.2)
Flovent HFA 44mcg	5.3 (0.1)	11.0 (0.2)
ProAir HFA	1.4 (0.1)	6.7 (0.1)
Proventil HFA	1.4 (0.1)	6.3 (0.1)
Qvar (BDP HFA)	1.7 (0.1)	4.7 (0.2)
Ventolin HFA	4.9 (0.1)	9.4 (0.2)

4. Conclusions

In this study, nine commercial MDI products were characterized by PDA via droplet velocity and size measurements. The sampling distance effects on droplet velocity and size were investigated. A comparison of two droplet size measurement techniques, PDA and LLS was performed. The relationship between droplet velocity and impaction force was discussed.

The PDA technique has been demonstrated to be a useful tool for characterizing MDI aerosol plumes, and provides important information for evaluating MDI drug delivery efficiency. Results from the evaluation of nine commercial products show that MDI droplet velocity can be used as a discriminative parameter for in vitro testing of MDI products and could be an important parameter for evaluation of in vitro equivalence in support of formulation or manufacturing changes and in evaluation of abbreviated new drug applications (ANDAs) for MDIs.

Although PDA appears to be sufficient for velocity analysis, its number based nature and limitation in measurement volume suggests that PDA is not a suitable droplet/particle size analysis tool for inhalation drugs.

PDA measurements provide more insightful information about the aerosol plume when combined with other MDI parameters. Obtained simultaneously with velocity via PDA measurements, the droplet size is another important indication for MDI aerosol drug delivery performance. Impaction force is the most noticeable characteristics perceived by a patient. By combining those measurements at different spray distances, it is feasible to observe the evolution of the MDI aerosol.

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