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Multimodal Particle Size Distributions Emitted From HFA-134a Solution Pressurized Metered-Dose Inhalers

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ABSTRACT

The purpose of this research was to investigate the measurement and in vitro delivery implications of multimodal distributions, occurring near or in the respirable range, emitted from pressurized metered-dose inhalers (pMDIs). Particle size distributions of solution pMDIs containing hydrofluoroalkane-134a (HFA-134a) and ethanol were evaluated using 2 complementary particle-sizing methods: laser diffraction (LD) and cascade impaction (CI). Solution pMDIs were formulated from mixtures of HFA-134a (50%-97.5% wt/wt) and ethanol. A range of propellant concentrations was selected for a range of vapor pressures. The fluorescent probe, Rhodamine B, was included for chemical analysis. The complementary nature of LD and CI allowed identification of 2 dominant particle size modes at 1 and 10 μm or greater. Increasing propellant concentrations resulted in increases in the proportion of the size distributions at the 1-μm mode and also reduced the particle size of the larger droplet population. Despite significant spatial differences and time scales of measurement between the particle-sizing techniques, the fine particle fractions obtained from LD and CI were practically identical. This was consistent with LD experiments, which showed that particle sizes did not decrease with increasing measurement distance, and may be explained by the absence of significant evaporation/disintegration of larger droplets. The fine particle fractions (FPFs) emitted from HFA-134a/ethanol solution pMDI can be predicted on the basis of formulation parameters and is independent of measurement technique. These results highlight the importance of presenting particle size distribution data from complementary particle size techniques.

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KEYWORDS: metered-dose inhaler, particle size distribution, laser diffraction, HFA-134a, cascade impaction, atomization

INTRODUCTION

Metered-dose inhalers are commonly used for the administration of therapeutic agents to the respiratory tract. However, since the ratification of the Montreal protocol in 1987, and the phaseout of chlorofluorocarbon (CFC) propellant systems, alternative propellant systems have been required to ensure this drug delivery system remains available to patients. The first alternative propellant to have full-term toxicity testing was hydrofluoroalkane (HFA) 134a.[1] Currently, several marketed products contain HFA-134a, including QVAR (beclomethasone dipropionate, 3M Pharmaceuticals, Minneapolis, MN) and Ventolin HFA (albuterol, GSK Inc, RTP, NC). The similarities and differences between CFC systems and the HFA counterparts have been reviewed elsewhere.[2] It is clear that HFA-134a is not a "drop-in" replacement for CFC-12 (**Table 1**). In fact, the transition to HFA-134a-based propellant systems has resulted in the identification of several incompatibilities with other traditional excipients, canister components, and valve elastomers.[2-4] These issues are generally related to the different solvency properties of HFA-134a compared with CFC-12. The different solvency properties of HFA-134a also influence drug solubility properties, allowing the formulation of solutions rather than suspension systems, which were frequently employed with CFC propellants. Solution systems offer the advantages of improved performance and uniformity because of drug homogeneity and physical stability but have increased potential for physical degradation.[5]

Significant particle size changes have also been noted in the transition from CFC-based systems to HFA-based formulations.[6-8] Several mechanisms for this observation have been proposed: (1) vapor pressure and energetic factors,[2] (2) pre-atomization and rapid propel-

Table 1. Composition of the Model Solution Formulations*

Formulation	HFA-134a % wt/wt	Ethanol % wt/wt	Rhodamine B % wt/wt
A	97.5	2.49	0.01
B	90.0	9.99	0.01
C	80.0	19.99	0.01
D	50.0	49.99	0.01

*HFA-134a indicates 1,1,1,2-tetrafluoroethane.

lant nucleation in the atomizer,[9] and (3) increased evaporation rates.[10] The significance of particle size changes is readily observed in the altered deposition patterns of medicinal aerosols. However, the mechanism of particle size changes resulting from the transition from CFCs to HFAs has not been widely explored other than to observe the phenomenon in the context of known physicochemical characteristics. Vapor pressure of pressurized metered-dose inhaler (pMDI) formulations has significant effect on the emitted particle size.[11] The vapor pressure, relative to atmospheric pressure, can be used as an indicator of the energy propulsion from the pMDI device that occurs during the atomization process. Increasing the ethanol concentration results in a decrease in the vapor pressure of the HFA-134a solution formulation.[2,12,13] There is also a positive deviation from ideality. This deviation implies that, in a binary mixture, components favor cohesive molecular associations with like molecules rather than adhesion with a second species.[14] It has been suggested that because of the positive deviation from Raoult's Law, addition of ethanol to HFA-134a may not reduce vapor pressure significantly. Consequently, there may not be an adverse influence on the emitted droplet size.[2]

Recently it was observed that HFA solution formulations displayed multimodal particle size distributions.[15] The present study explores the implications of formulation factors of solutions of HFA-134a/ethanol pMDIs with particular reference to the changes in the particle size distribution. Specifically, multimodal droplet size distributions obtained by increasing the proportion of ethanol in solution formulations were investigated.

MATERIALS AND METHODS

Pressurized Metered-Dose Inhaler (pMDI) Manufacture

A series of solution pMDIs were prepared using the propellant 1,1,1,2-tetrafluoroethane (HFA-134a; Aeropress, Shreveport, LA) with ethanol (Aaper Alcohol and Chemical Co, Shelbyville, KY). Specific quantities of each component in the pMDIs are shown in **Table 1**. Aliquots of the nonvolatile solutions (fluorescent probe dissolved in ethanol) were dispensed gravimetrically to epoxy-coated aluminum aerosol canisters (Cebal, Springfield, NJ). Metered-dose valves (25-µL volume, Bespak, Apex, NC) were immediately crimped onto each can, and the canister was filled with the desired weight of HFA-134a through the valve using a propellant compressor pump (Pamasol model P2005, Pamasol Willi Mäder AG, Pfäffikon, Switzerland) and a small-scale crimping and pressure filling machine (Pamasol model P2008) or a pressure burette and manual canister crimper (Aerotech, Maryland, NY). All canisters were prepared on a single day and were used within 1 month of manufacture. A 0.33-µm actuator (Bespak) was used for all experiments.

Particle Size Analysis

Laser Diffraction (LD) Studies

Droplet size and obscuration were measured using a laser diffraction instrument (2600 c, Malvern, Southborough, MA, or Sympatec Inc, Princeton, NJ)). The influence of spatial and temporal changes on particle size was also investigated. The pMDI was positioned at 2, 3, 4, 6, and 8 cm from the laser beam and fixed at a height (the aerosol plume center was projected across the laser). A number of time points after pMDI actuation were selected to compare the formulations throughout their passage through the laser region. The aerosol device was positioned such that the actuator orifice was within the lens cut-off distance, the device did not deposit aerosol droplets on the detector lens surface, and the actuator orifice was aligned with the height of the laser path. Particle size and optical concentrations were determined in each experiment. Particle size and distribution were determined assuming Fraunhofer diffraction theory. Mie theory accurately calculates small particle sizes from laser diffraction data because of the completeness of the theory

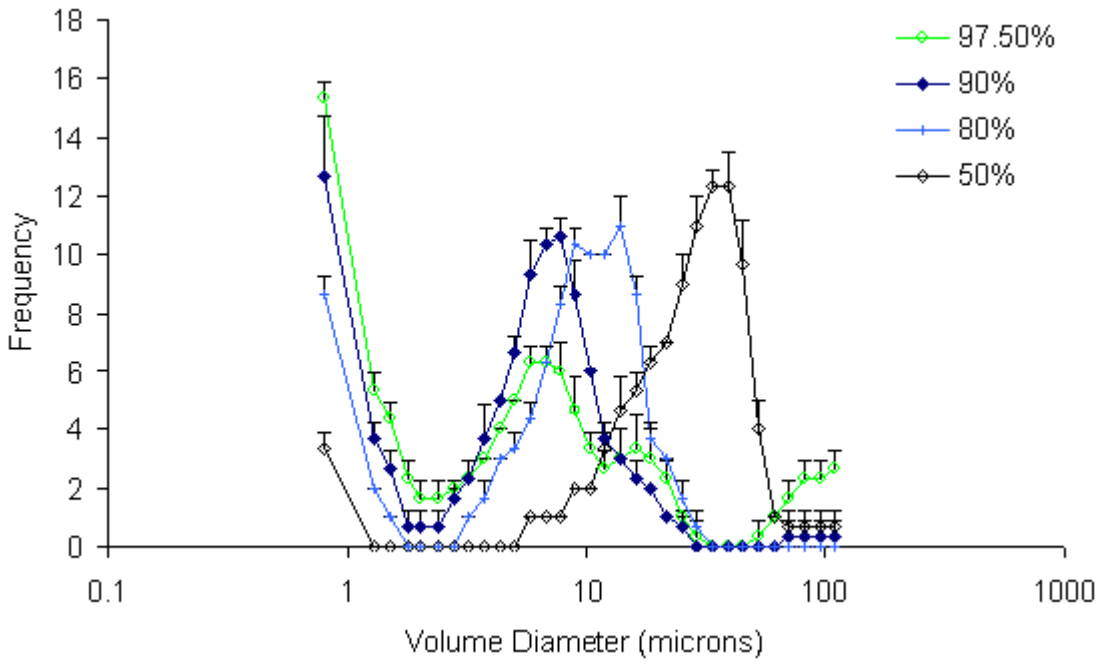


Figure 1. Multimodal particle size distributions obtained from HFA-134a/ethanol pMDIs determined using laser diffraction (Malvern instrument) (mean ± SD, n = 3).

describing light diffraction and refraction. However, in order to use this theory, knowledge of the refractive indices of the particles and the medium is required. If this is not known accurately, calculations have no more validity than the Fraunhofer approximation. Thus, in each laser diffraction study the Fraunhofer theory was employed. The influence of propellant vapor on laser light diffraction patterns was also investigated using inverted pMDI canisters containing HFA-134a and employing continuous valves. During data collection, these canisters were actuated at various distances from the laser beam using the LD instrument. The influence of the propellant vapor (without liquid droplets) on effects such as beam steering was investigated. Data analysis was performed by transferring particle size distribution data into an Excel spreadsheet (Office 2000, Microsoft, Bellevue, WA). Graphical and distribution analyses were then performed.

Cascade Impaction (CI) Studies

The aerodynamic particle size analysis of the aerosol formulations was conducted using an Andersen 8-stage nonviable inertial impactor (Graseby-Andersen, Smyrna, GA) fitted with a United States Pharmacopeia (USP) sampling inlet.[16] A flow rate of 28.3 L/min was drawn through the apparatus. Droplets were impacted on collection stages with cutoff diameters of 9.0, 5.8, 4.7, 3.3, 2.0, 1.1, 0.7, and 0.4 µm, and the absolute filter (0.22 mm). The metering valves were primed by discharging 3 shots to waste. The pMDIs were actuated 5 times into the Andersen Impactor. The pump was switched on for 5 seconds prior to MDI discharge. There was a pause of 10 seconds after each individual discharge to allow complete deposition and clearance from the impactor. Data were presented graphically. Median diameters were determined. Since data did not conform to a log normal distribution, geometric standard deviations were not calculated.

Chemical Analysis

The fluorescent species (Rhodamine B, Sigma Chemical Corp, St Louis, MO) used in this study was employed as a trace marker in the formulations because it is readily detectable using fluorimetry at ng/mL concentrations. The fluorescence assay was validated for linearity and reproducibility.

RESULTS AND DISCUSSION

Multimodal Particle Size Distributions

Figure 1 shows the multimodal particle size distribution of aerosols (measured using Malvern instrument) emitted from pMDIs containing the formulations A

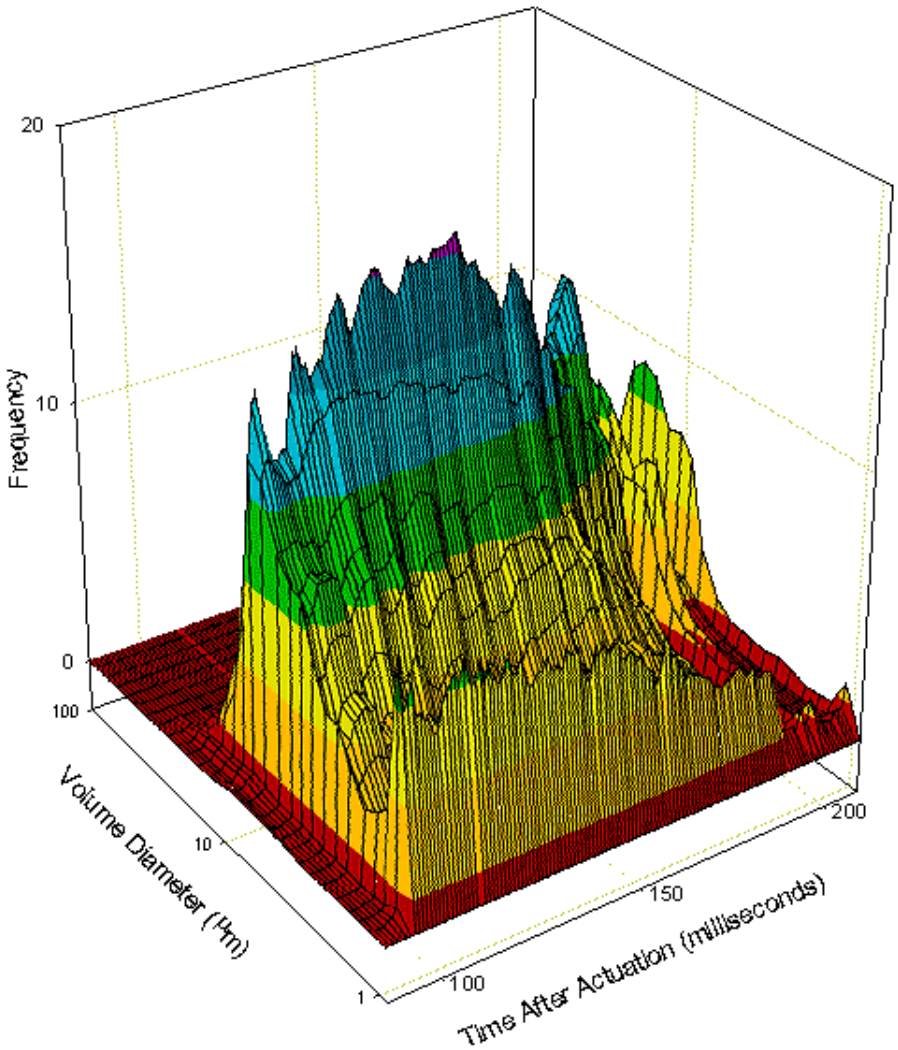


Figure 2. Example of particle size distribution changes of an HFA-134a (90% wt/wt) and ethanol (9.99%) aerosol plume over time (Sympatec instrument).

through D (**Table 1**). The multimodal distribution for each formulation is generally located in the same range of particle size. The prominent modes appear at approximately 1-µm diameter and at approximately 10 µm. There are additional shoulders in the data indicative of unresolved additional particle populations. However, for the purpose of discussion, this complex distribution will be assumed to have a predominantly bimodal nature. The optical cutoff of the Malvern instrument is 1 µm, preventing the accurate location of the lower mode of the particle size distribution using this instrument. The Sympatec instrument, which was also used (**Figure 2**), has an optical cutoff at around 0.9 µm. Particle size distributions obtained from the Sympatec instrument suggest that few particles were present below 0.9 µm (**Figure 2**). CI analysis confirmed the bimodal distribution (**Figure 3**). In addition, the mode located at approximately 1 µm was also confirmed by the higher resolution of inertial impaction at this size range.

Figure 4 illustrates the particle size results calculated from pure vapor emission from a pMDI through the laser. Vapor results in areas of different refractive index and leads to bending of the incident light at small angles. The refraction of light at small angles causes the detection of laser light on the inner rings of the instrument and these are then erroneously calculated to be large particles (larger particles scatter light at smaller angles).

The presence of a predominantly bimodal distribution is significant because the 2 particle populations exist at sizes that are aerodynamically important for regional

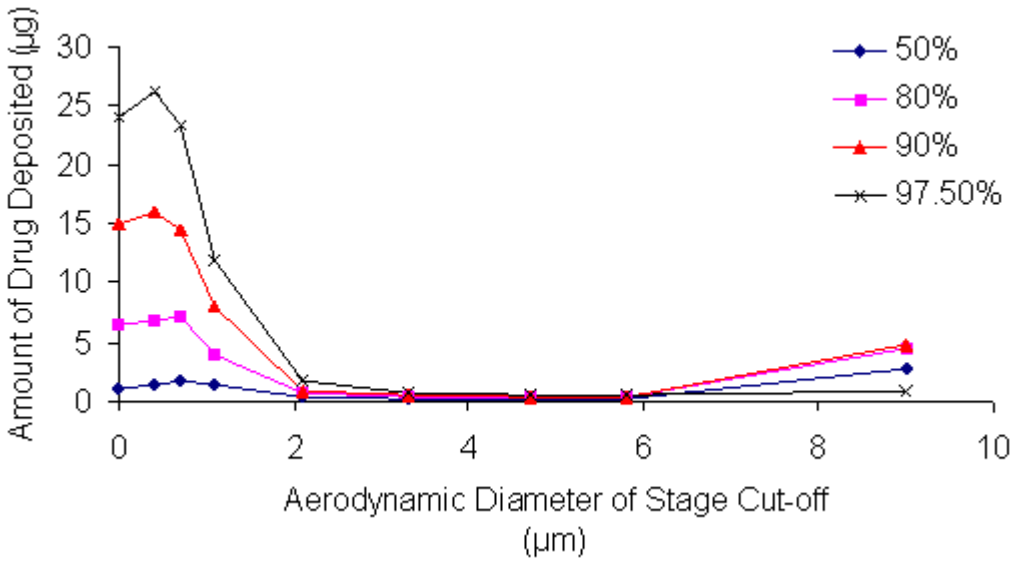


Figure 3. Summary of CI particle size data for varying percentages of HFA-134a propellant (mean ± SD, n = 3).

deposition in the respiratory tract. The larger size population exists at approximately 10 µm and above. This size is generally accepted to be "nonrespirable" and will tend to deposit in the oropharyngeal and upper regions of the respiratory tract. The second population of particles is distributed around a diameter of approximately 1 µm and is considered to be "respirable." This complex particle distribution must be evaluated if the aerosols emitted from pMDIs are to be optimized. The influence of ethanol concentration in the formulation on the emitted aerosol particle size distribution was investigated. All of the formulations had significant droplet populations at 1 µm. The proportion of 1-µm droplets increased with increasing propellant concentrations. **Figure 4** describes the individual stage deposition (from CI studies) for each formulation. These observations show that the mode of the small particle population was unchanged when the formulation was modified. However, the general effect of increasing ethanol on the larger population of droplets (≥10 µm) was to shift the mode to larger droplet sizes (**Figure 2**) and to increase the proportion of these larger droplets.

A third significant mode (approximately 100 µm) detected in the most propellant-rich formulations was an artifact arising from high levels of propellant vapor. This was determined using inverted pMDI canisters to blow propellant vapor across the laser beam in the absence of liquid droplets. The influence of the propellant vapor on the laser light was significant at close distances. High propellant levels cause a local change in the refractive index, resulting in beam steering.[17]

Multimodal particle size distributions may have an influence on the delivery of drug to certain regions of the lung. It appears that a significant proportion of the dose delivered by the pMDI containing HFA-134a/ethanol solution formulations was atomized to a state that is not generally considered respirable (>6 µm). Increasing propellant concentrations resulted in greater proportions of droplets that might be considered "respirable." The proportion of these respirable droplets is an important factor in calculating the dose delivered to the lungs. Changes to the particle size population located in the 1-µm region may also influence regional lung deposition. However, this possibility requires further investigation using in vivo techniques.[18] Decreasing the propellant concentration also altered the population of droplets present at the nonrespirable range (≥10 µm). This change may also influence the performance of HFA-134a/ethanol solution systems. At high propellant concentrations, this mode is located at approximately 10 µm and may undergo evaporation or further disintegration such that these particles enter the respirable range (ie, become smaller). However, at lower propellant concentrations, this population of droplets tends to shift to larger droplet sizes and, therefore, may not change in size sufficiently to become respirable. Laser diffraction experiments, investigating spatial and temporal changes in particle size, were initiated to explore this issue.

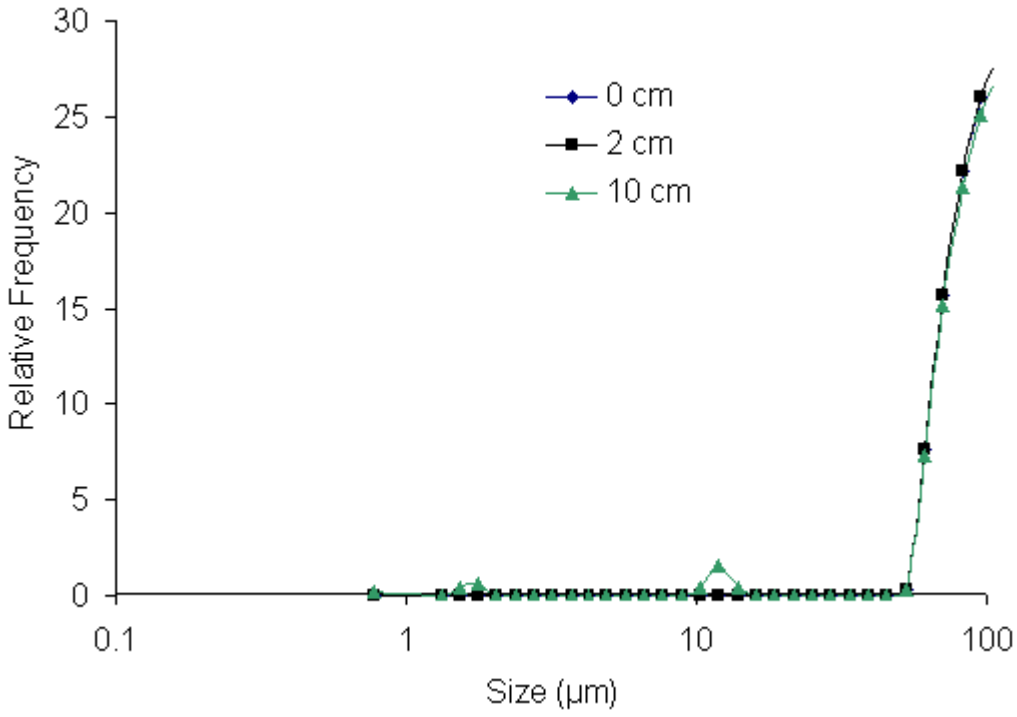


Figure 4. Examples of particle size results from vapor-only emission from an inverted pMDI placed at different distances from the laser sensing zone of the Malvern instrument. Small angle light refraction leads to erroneous particle size determinations (large particle population at 100 µm).

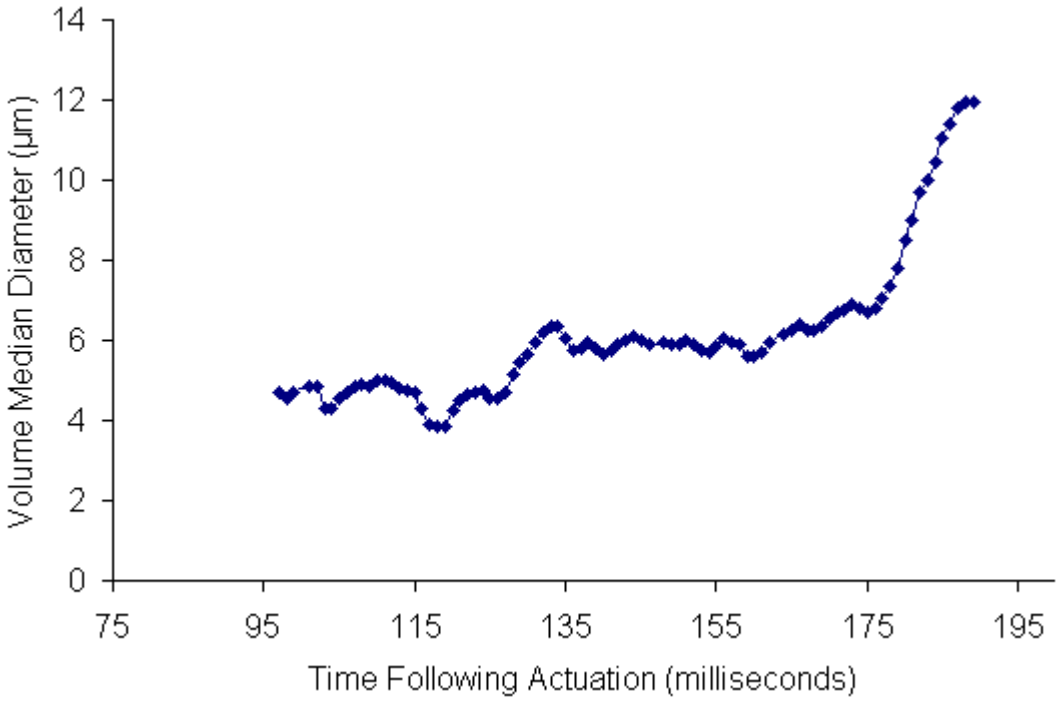
Effect of Time

Laser diffraction methods allow collection of time resolved data. Since the metered dose is emitted rapidly, temporal analyses may yield greater detail with respect to the processes by which aerosol particle size distributions are produced. **Figure 2** illustrates a typical example of the changes to the particle size distribution as a function of time during the firing of the pMDI (Sympatec instrument). Similarly with each formulation tested, the bimodal distribution was present throughout the lifetime of the plume as it passed through the laser sensing region. At the terminal end of the plume (longer times) the small droplet population tended to decrease relative to the larger droplet population.

Figure 5 summarizes the effect of these changes to the particle size distribution by looking at the median diameter (by volume). The volume median diameter (VMD) increases dramatically at the tail of the plume. Explanations of this phenomenon have been suggested in the literature: (1) metering chamber and propellant cooling,[19,20] (2) differences in propellant evaporation rates in vapor-saturated or propellant-cooled regions (body/tail),[21] and (3) differential evaporation of finer droplets (Kelvin effect).[21]

Effect of Distance

Similarly, the influence of the distance at which laser diffraction measurements are made was investigated. The VMD was determined for 3 arbitrarily defined regions of the aerosol plume: the front edge (the initial 5 milliseconds of the plume when the optical concentration was greater than 1%); the body (5-millisecond region when plume optical concentrations were highest); and the tail (the final 5 milliseconds when the optical concentration was greater than 1%). Increasing the measurement distance did not significantly alter the VMD of the front and body portions of the plume (**Figure 6**). This finding indicates that, in these regions, droplet evaporation was minimal. However, the VMD of the tail region of the plume demonstrated appreciable decreases with increasing measurement distance. This observation correlates well with the theory postulating that the increase in droplet size at the end of the metered spray (**Figure 5**) results from the cooling of the actuator and propellant. Hence, the decrease in



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droplet size of the tail region of the plume with increasing distance is likely to be due to evaporation.

However, for much of the aerosol plume (front edge and body), evaporative effects on emitted droplets appear insignificant up to approximately 10 to 12 cm away from the actuator orifice. The implication of this observation for pulmonary delivery is that large droplet size populations (located at approximately 10 µm) will not evaporate sufficiently to enter the "respirable" range before the aerosol plume impacts in the oropharynx.

Particle size changes as a function of ethanol concentration were also observable when analyzed using CI (**Table 2**). Increasing ethanol concentrations significantly increased the mass median aerodynamic diameter (MMAD) between formulations ($P < .05$). This increase in MMAD is due to the decrease in energy available for atomization as propellant concentrations decrease (as indicated by vapor pressure differences) and also to the presence of greater proportions of nonvolatile components (ethanol) in the spray as ethanol concentrations increase. An empirical model for this effect has been described[19]:

$$MMD = \frac{8.02}{Y_{vap}^{0.56}\left[\frac{p_{ec} - p_{amb}}{p_{amb}}\right]} \quad (2)$$

where Y_{vap} is the vapor mass fraction in the expansion chamber; P_{ec} is the pressure in the expansion chamber; and P_{amb} is the ambient pressure (ie, an increase in vapor pressure should correspond to decreases in droplet size).

Comparisons Between Laser Diffraction and Cascade Impaction

Comparisons between particle size data obtained from LD and CI often show marked differences.[22,23] This is particularly the case with unstable and transient sprays emitted from pMDIs.[23] The CI MMAD values were several factors smaller than the corresponding VMDs calculated from LD experiments (**Table 2**). This observation has been reported previously and has been related to the different spatial and temporal methods of particle size measurement.[23] Specifically, CI analysis involves a "throat" and entraining airflow, and the uppermost stage has an aerodynamic cutoff of 9 µm.

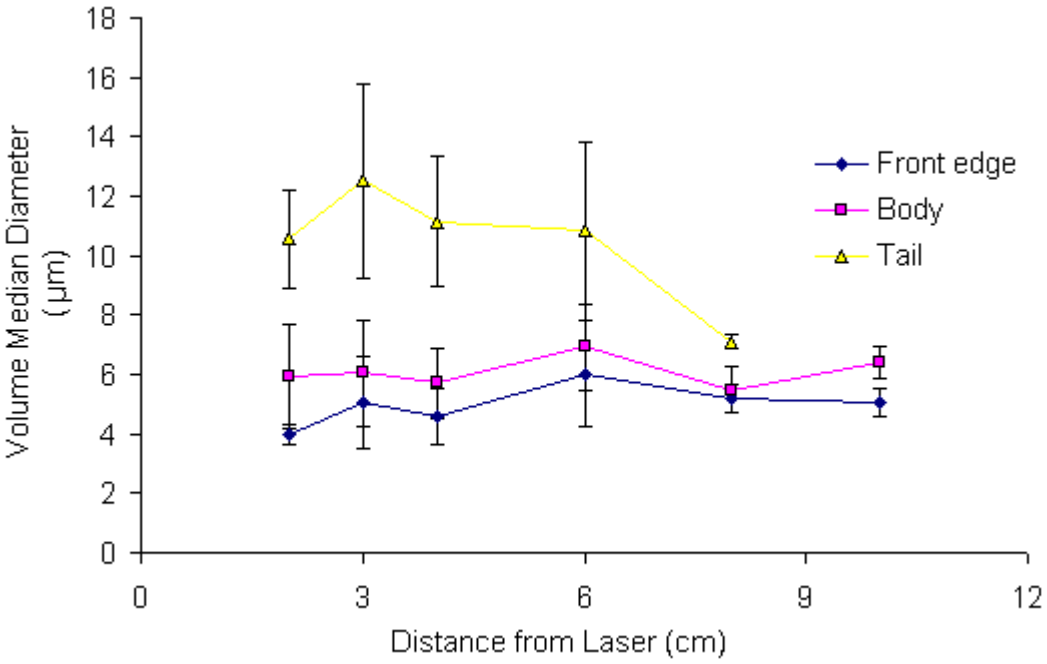

Figure 6. Effect of measurement distance on the VMD of aerosol droplets emitted from an HFA-134a pMDI. (Front edge is the initial 5 milliseconds of the plume when the optical concentration was greater than 1%; body is the 5-millisecond region, when plume optical concentrations were highest; and tail is the final 5 milliseconds when the optical concentration was greater than 1%, Malvern instrument) (mean ± SD, n = 3).

Table 2. Summary of Median Diameters and Fine Particle Fractions Calculated From Cascade Impaction and Laser Diffraction Studies*

	Formulation:	**97.5% HFA-134a**		**90% HFA-134a**		**80% HFA-134a**		**50% HFA-134a**	
		Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
Median diameter	Cascade impaction	0.48	0.02	0.55	0.04	0.69	0.09	1.54	0.31
	Laser diffraction†	5.68	0.27	6.15	0.16	9.82	0.49	28.53	1.43
Fine particle fraction	Cascade impaction	0.51	0.14	0.34	0.02	0.18	0.02	0.05	0.0
	Laser diffraction†	0.53	0.02	0.37	0.03	0.18	0.07	0.05	0.00

* HFA-134a indicates 1,1,1,2-tetrafluoroethane.
† Laser diffraction results are from the Malvern instrument.

These factors are likely to cause significant deviation from the particle size as measured by LD that were made 6 cm from the actuator orifice without the geometrical constraints of the USP throat inlet or the entraining airflow. For the highly dynamic aerosol emitted from a pMDI, both time and space are critical parameters that may influence the measurement of particle size.

However, if the particle size distributions are considered for comparison rather than the median diameters, good agreement is obtained. **Table 2** summarizes the CI and LD data. Comparisons of the fine particle fractions (FPF—fraction of emitted dose that is less than 5 µm) for each formulation using the respective particle sizing techniques are essentially identical. The FPFs were determined over the entire optical size range of the LD instrument (ie, up to 108 µm diameter) and are,

therefore, directly comparable to the FPF calculated from typical CI setups. This observation indicates that the FPFs of HFA-134a/ethanol solution formulations are not significantly influenced by measurement technique differences, including principles of measurement, sampling, airflow, and the timescales of measurement. This comparison of FPFs also confirms the earlier observations that (1) the particle size distribution is predominantly bimodal, and (2) the evaporation of droplets in significant regions of the plume is minimal. Therefore, the second droplet population at 10 μm or more does not evaporate or disintegrate sufficiently to enter the respirable range, regardless of the propellant composition. These observations also illustrate the importance of presenting entire distributions rather than median diameters of distributions.

Importance of Bimodal Distribution for pMDI Formulation and Design

The general goal of the formulator is to optimize the pMDI aerosol such that throat deposition is minimized while lung deposition is maximized and well controlled. Thus, optimization of the bimodal particle size distribution emitted from a pMDI involves decreasing the relative proportion of the large particle population with respect to the small "respirable" droplet population. In addition, subtle changes in the small droplet population may lead to differences in regional lung deposition. Aerosols with greater peripheral deposition may not have corresponding (ie, linear) increases in pharmacodynamic effects.[24-26] Thus, regional deposition must also be investigated. In this study, the presence of a predominantly bimodal particle size distribution will directly influence optimization of HFA-134a/ethanol pMDIs.

First, the fine particle fraction emitted from the pMDI can be increased by using higher concentrations of propellant in the formulation. However, increasing propellant concentrations must also be weighed against other factors such as solubility, stability, and compatibility with other components of the pMDI.[2]

Second, the fine particle fraction produced by each formulation appears to be independent of processes that may further alter particle size (evaporation and secondary breakup of droplets). **Figure 4** shows that the small particle populations do not change when the formulation is modified. This would appear to be quite significant for in vivo lung deposition patterns, as the uniformity of performance may correlate with predictable regional deposition. Studies have been initiated to challenge this hypothesis and will be the subject of a future publication.

Third, in HFA-134a/ethanol solution pMDIs, the use of add-on devices such as spacers and holding chambers may have limited utility. This hypothesis is derived from observations that show the larger droplet population is insignificantly influenced by evaporative or disintegration processes after atomization. Therefore, the primary function of spacers in these systems may only be to capture those droplets that may have otherwise deposited in the oropharyngeal regions of the airways. It is not expected that the larger droplet population present in the aerosol plume will decrease in size inside the spacer to allow them to be delivered to the lungs. This hypothesis is the subject of further studies.

Mechanism of Multimodal/Bimodal Distributions

The mechanisms of atomization in HFA-134a pMDIs have not been widely explored in the literature. Two hypotheses for atomization have been recognized: (1) internal flash evaporation,[9] and (2) aerodynamic breakup.[19] It is well known that primary droplets can break up into smaller secondary droplets. This type of phenomenon often results in multimodal or bimodal droplet size distributions.[21] Primary droplet formation can be followed by secondary breakup if the changes in relative velocity are sufficient.[21,27] The aerodynamic loading on HFA-134a droplets is predicted to be quite high (shear or catastrophic breakup) according to regimes suggested by Faeth et al.[28] Empirical predictions of secondary particle size during "bag breakup" are estimated to be approximately 0.042 times the diameter of the primary droplet.[21] Thus, application of this rule to the larger droplet population yields the following for formulation A (97.5% wt/wt propellant): 10 μm represents the primary droplets and 0.42-μm droplet size is predicted for the secondary droplets. These 2 droplet sizes match well with those determined by both LD and CI studies (**Figures 2** and **4**), suggesting the origin of the predominantly bimodal distribution may be a secondary droplet breakup phenomenon.

Quantitative prediction of flow or primary droplet sizes is not currently possible because of the complexity of unsteady multiphase fluid dynamics that occurs in pMDIs.[21] Observations made by Dunbar et al[9,20] and calculations made by Finlay[21] have demonstrated that an aerosol emitted from a pMDI (HFA-134a propellant) has only a small proportion of its volume occupied by droplets. This implies that HFA-134a aerosols are pre-atomized. These observations are consistent

with the observations that suggest that atomization appears to have already occurred by the time the aerosol plume reaches the laser sensing region of the laser diffraction instrument and the impaction plates of the Andersen Cascade Impactor (ACI). In addition, calculations of postnozzle breakup of HFA-134a droplets with initial relative velocities of around 200 milliseconds-1 indicate that a 10-μm droplet will undergo breakup before it has traveled 4.1 cm from the orifice.[21] Droplets of similar size, traveling at lower initial relative velocities may not undergo breakup. The closest distance measurable in the studies using laser diffraction was approximately 4 cm. Furthermore, the addition of a vapor pressure suppressant such as ethanol is likely to reduce the initial relative velocities. Thus, these theoretical considerations agree with the experimental observations and allow speculation on the mechanisms by which these particle size distributions were formed.

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CONCLUSSION

Multimodal particle size distributions emitted from pMDIs containing HFA-134a and ethanol contained 2 dominant particle size modes important for respiratory delivery. Increasing propellant concentrations correspond to increased FPFs. The mode of the fine particles remained constant despite changing formulation and measurement parameters (time, distance, and entraining airflow). Droplets that constitute the larger mode in the particle size distribution (approximately 10 μm) exhibited insufficient evaporation and disintegration with respect to distance and time after actuation to become "respirable." Therefore, FPFs emitted from HFA-134a/ethanol solution pMDIs can be predicted on the basis of formulation parameters and are independent of measurement technique. This study also highlights the importance of presenting particle size distribution data rather than median diameters for metered-dose inhaler products.

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