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Application of USP Inlet Extensions to the TSI Impactor System 3306/3320 Using HFA 227 Based Solution Metered Dose Inhalers

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ABSTRACT The objective of this study was to further evaluate the need for a vertical inlet extension when testing solution metered dose inhalers using the TSI Model 3306 Impactor Inlet in conjunction with the TSI Model 3320 Aerodynamic Particle Sizer (APS). The configurations tested using the TSI system were compared to baseline measurements that were performed using the Andersen Mark II 8-stage cascade impactor (ACI). Seven pressurized solution metered dose inhalers were tested using varied concentrations of beclomethasone dipropionate (BDP), ethanol, and HFA 227 propellant. The inhalers were tested with the cascade impactor, and with the TSI system. The TSI system had three different configurations as the manufacturer provided (0 cm) or with inlet extensions of 20 and 40 cm. The extensions were located between the USP inlet and the Model 3306 Impactor Inlet. There were no practical differences between each system for the stem, actuator, or USP inlet. The fine particle mass (aerodynamic mass <4.7 μm) was affected by extension length and correlated well with the ACI when an extension was present. APS particle size measurements were unaffected by the extension lengths and correlated well to particle size determined from the ACI analysis. It has been confirmed that an inlet extension may be necessary for the TSI system in order to give mass results that correlate to the ACI, especially for formulations having significant concentrations of low volatility excipients. Additionally, the results generated from this study were used to evaluate the product performance of HFA 227 based solution formulations that contain varying concentrations of ethanol as a cosolvent.

KEYWORDS Metered dose inhaler, HFA 227, Cascade impactor, APS

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INTRODUCTION

Inhalation therapy has had a significant impact in treating respiratory diseases such as asthma and emphysema (Dipiro et al., 1999). Two important factors for delivering a drug via inhalation include the aerodynamic particle size and the fine particle mass. First, aerosolized particles containing a drug must be of proper particle size to ensure the drug efficiently gets to the site of action. Second, and directly related to the particle size distribution, an adequate mass of drug must be delivered to the target site. As a result, early formulation and device screening is paramount for the development of an inhalation drug delivery device.

The Andersen Cascade Impactor (ACI) has long been a "standard" to measure performance of pressurized inhalers. While the ACI is effective, it is also time and labor intensive. As a result, several researchers have evaluated alternative instruments for characterizing pharmaceutical aerosols (De Boer et al, 2002a, 2002b; Kamiya et al., 2004, Kwong et al., 2000; Mitchell et al., 2003). The TSI 3306 as shown in Fig. 1 (TSI Aerodynamic Particle Sizer Model 3320/

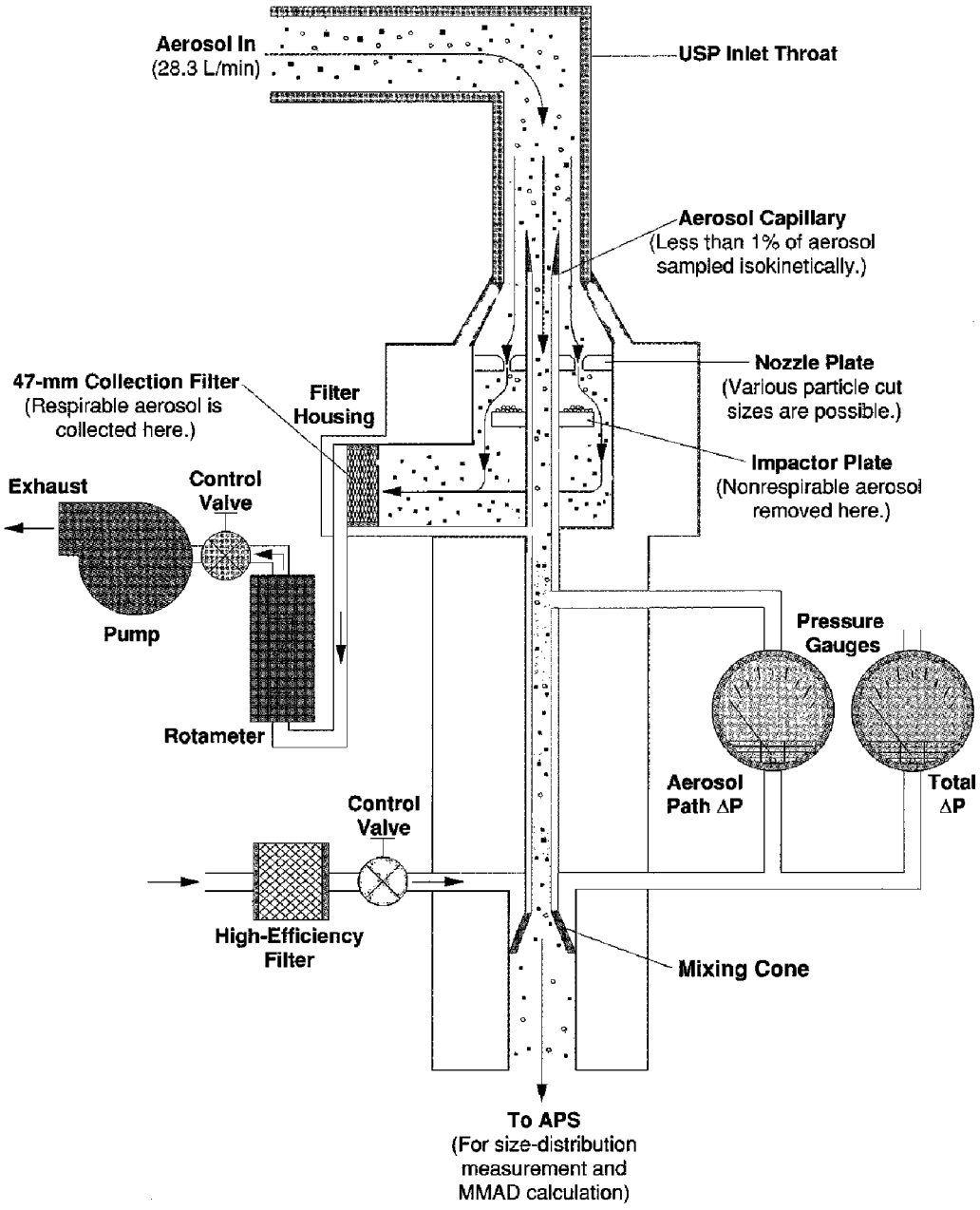

FIGURE 1 Schematic of the TSI 3306 Impactor Inlet as Supplied by the Manufacturer (0 cm Extension).

3321 with the TSI Impactor Inlet Model 3306, TSI Inc., Shoreview, MN) is being investigated as a tool for generating similar performance data in real time (for aerodynamic particle size) and with less labor involved for obtaining fine particle mass (Gupta et al., 2002; Myrdal et al., 2002; Stein et al., 2002, 2003). Previous studies have suggested the use of an inlet extension with the TSI system in order to obtain results that correlate with the ACI (Mitchell et al., 2003; Myrdal et al., 2004a).

This study was conducted to investigate the need for an extension with the use of the TSI system in order to correlate to the Andersen Mark II Cascade Impactor (ACI, Graseby-Andersen, Inc., Smyrna, GA) for HFA 227 (1,1,1,2,3,3,3-heptafluoropropane) based solution formulations containing ethanol as solubilizer for the active drug substance. Seven pressurized metered dose inhalers (pMDI) were evaluated with different concentrations of beclomethasone dipropionate (BDP) as active drug substance, ethanol, and HFA 227. These formulations were tested using the TSI system as the manufacturer provided (0 cm extension), as well as with a 20 cm extension, and a 40 cm extension as previously described (Myrdal et al., 2004a). Results for the TSI configurations were compared to those measurements obtained from ACI testing. To investigate differences in the systems, residual ethanol testing was performed to evaluate the presence of unevaporated ethanol in droplets that collected on the impactor plate.

MATERIALS AND METHODS

Materials

Solution formulations containing 0.08% or 0.4% w/w of BDP (provided by 3M Drug Delivery Systems, St. Paul, MN), 200 proof ethanol (Aaper Alcohol and Chemical Company, Shelbyville, KN) in concentrations of 5%, 10%, 15%, and 20% w/w, and HFA 227 (ICI Chemicals and Polymers Limited, Runcorn, Cheshire, UK) were prepared in pressure resistant glass vials (Wheaton Glass, Mays Landing, NY) with 50 mcL Spraymiser™ (3M Drug Delivery Systems) metered valves. These formulations were sonicated until a clear solution was present (~1 minute), and inspected with a hand-held laser to ensure no solid particles remained. One combination was insoluble and therefore excluded from the study (0.4% BDP, 5% ethanol). All testing utilized the same QVAR™ actuator (0.3 mm diameter orifice), which was also provided (3M Drug Delivery Systems). All other solvents were obtained from Aldrich Chemical Company (Milwaukee, WI) and were used as received.

Testing Methods

Prior to testing, each pMDI was actuated three times and the valve and stem washed with methanol. Between runs, each component was rinsed with methanol and allowed to dry before the next experiment. Each inhaler was tested in triplicate on the ACI as well as the TSI system (0 cm, 20 cm, and 40 cm extensions). Five actuations were measured over 40 sec using the TSI system, and 5 actuations over 3 min using the ACI, both measured with an airflow rate of 28.3 liters per minute. For experiments run on the TSI system, the valve stem, actuator, USP inlet, inlet extensions (if used), impactor plate (4.7 μm cutoff, determined as plate deposition), and a filter (47 mm Glass Fiber Filter, Gelman Laboratory, Ann Arbor, MI) were rinsed with fixed volumes of 70:30 acetonitrile:water (v/v) [mobile phase for High performance liquid chromatography (HPLC) analysis] and quantified via HPLC with UV detection at a wavelength of 240 nm. The impactor plate of the TSI system was swabbed with a solvent soaked cotton swab. The filter solution was filtered (0.2 μm Acrodisc©, Pall Gelman Laboratories, Ann Arbor, MI) before analysis and represents the fine particle mass ($FPM_{4.7\ \mu m}$). A small portion of the aerosol (approximately 0.2%) is sampled isokinetically from the Model 3306 and presented to the 3320 for direct particle size measurement.

Equivalent methods were used for collection on the ACI; stem, actuator, USP inlet, stages 0–7, and filter were rinsed and quantified in the same manner. Fine particle mass for the ACI is defined as the mass of BDP collected from stages 3 through filter.

In order to investigate the relative concentration of liquid ethanol still remaining in the aerosol droplets, residual ethanol testing was performed on the TSI configurations. For this test, ethanol sensitive paper (Hewlett-Packard, Houston, TX, product number 5080-8735) was fitted over the impactor plate. Five actuations were then performed, according to the procedures defined above, for each of the four ethanol concentrations and three extension lengths.

RESULTS AND DISCUSSION

Stem and Actuator

There was a small and consistent percentage of BDP that remained on the stem upon actuation with a mean of 3.45%±0.62% of total drug collected. Drug collected from the actuator was also consistent, with a mean of 17.11%±1.74% of total drug collected. There was no trend with either the stem or actuator when examining the different extension lengths or when comparing varied concentrations of BDP and ethanol. In addition, there were no practical differences between the ACI and the TSI systems, which is not surprising since the stem and actuator were the same for all configurations.

USP Inlet

Figure 2 represents the drug deposited on the USP inlet for each configuration and formulation (standard deviations are not included for clarity purposes). The deposition on the USP inlet was consistent between each test configuration (TSI system 0, 20, and 40 cm, ACI) for each formulation. The correlation coefficient between each TSI configuration and the ACI are 0.99 with R^2 values greater than 0.94. The pair wise analysis of variance (ANOVA) of the TSI and ACI results for each formulation revealed that only three of the 21 configurations were significantly different ($p<0.05$). The three outliers were found to be isolated with no systematic trend apparent. While the TSI and the ACI utilize the same USP inlet, the results indicate that an extension of the inlet does not result in a significant change in pressure or airflow characteristics. Although there was no difference in the inlet deposition as a function of extension length, a correlation between percent ethanol in a given formulation and amount of BDP collected from the inlet was observed. As ethanol concentration increased from 5 to 20% w/w, inlet deposition increased from ~20% to ~50%, regardless of drug concentration. These findings are consistent with previously reported data by Gupta et al. (2003) for 134a based formulations.

Extensions

Adding vertical extensions between the USP inlet and the ACI inlet did not result in significant wall losses in this region. No quantifiable drug was found on the extensions in 36 of 42 trials performed. Of the six extensions with drug found, the range was 0.38%–2.94% of total recovery with a mean of 1.07%±0.94%. There was only one case in which there was an extension recovery greater than 1%. No trends were observed when examining extension length, drug, or ethanol concentration. Therefore, it appears that the extension does not adversely affect airflow dynamics and drug deposition on the extension can be considered negligible.

Fine Particle Fraction

Fine particle fraction was used as the principal parameter for comparison between the different configurations and systems. Fine particle fraction for the TSI Model 3306 (FPF_{TSI}) is defined as the fine particle mass relative to the total amount of drug

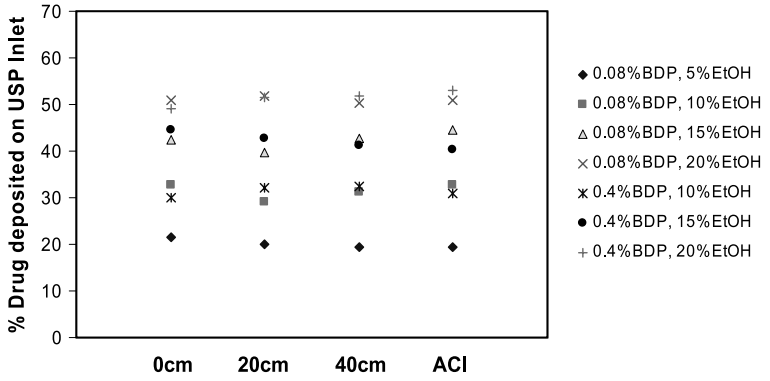

FIGURE 2 Percentage of BDP Collected from the USP Inlet for Each TSI System as well as for the Andersen Cascade Impactor (ACI).

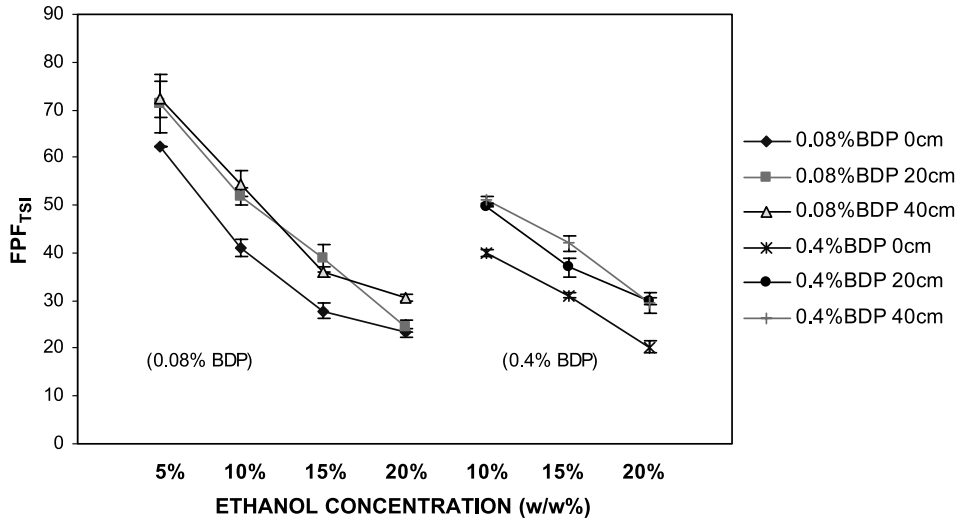

FIGURE 3 **Fine Particle Fraction as a Function of Ethanol Concentration for Each Drug Concentration, 0.08% and 0.4% BDP Shows the 0 cm Configuration with Lower FPF for Both Drug Concentrations.**

collected from the filter ($FPM_{4.7\ \mu m}$), impaction plate, and USP inlet, i.e.,

$$FPF_{TSI} = \frac{filter}{filter + plate + USP\ Inlet} \times 100$$

Figure 3 shows the FPF_{TSI}, for each formulation and extension length. The first series of data represent the formulations having 0.08% w/w BDP at 5, 10, 15, and 20% w/w ethanol. The second series of data is for the 0.4% w/w BDP formulations at 10, 20, and 20% w/w ethanol. As can be seen from both series, the FPF_{TSI} for the 0 cm extension length is consistently lower than the 20 and 40 cm configurations, regardless of the drug or ethanol concentration. The 20 and 40 cm configurations have fine particle fractions that are very similar for each formulation.

For the ACI, the fine particle fraction (FPF_{ACI}) is the total mass from impaction stage 3 through filter relative to the total drug collected ex-actuator, i.e.,

$$FPF_{ACI} = \frac{Stages\ 3 \rightarrow filter}{Stages\ 0 \rightarrow filter + USP\ Inlet} \times 100$$

To facilitate the evaluation of the two instruments, the ratio the TSI fine particle fraction, FPF_{TSI} to the ACI value, FPF_{ACI}, can be compared,

$$ratio\ TSI/ACI = \left[\frac{FPF_{TSI}}{FPF_{ACI}}\right] \times 100$$

Figure 4 shows the TSI/ACI ratio for each formulation and the three extension lengths. For a given formulation, FPF_{TSI} was compared to its

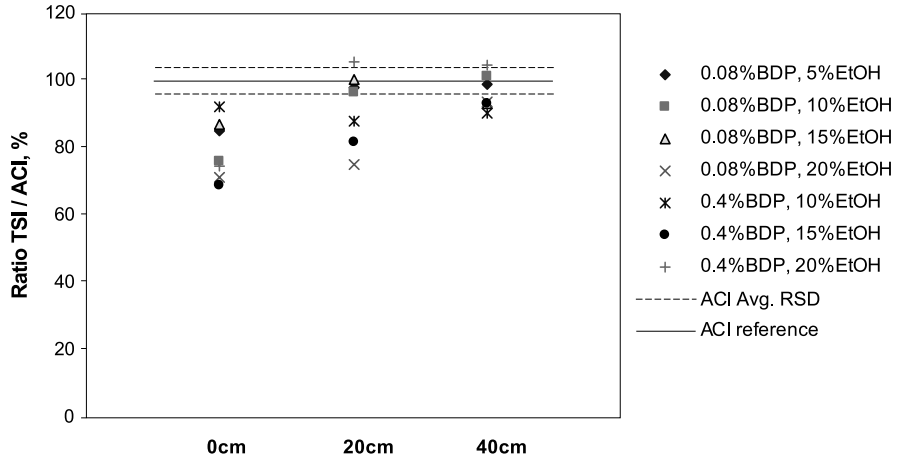

FIGURE 4 **Fine Particle Percent Collected from the TSI System, at Different Extension Lengths (0 cm, 20 cm, and 40 cm) Relative to the ACI Value for the Identical Formulation. 100% Represents the ACI Percent Fine Particle Mass for Each Formulation.**

corresponding FPF_{ACI} (=100%) for each configuration (0, 20, and 40 cm). The solid horizontal line represents equivalent results from each instrument (e.g., $FPF_{TSI}=FPF_{ACI}$). The dashed horizontal lines indicate the average standard deviation from the FPF_{ACI} results, indicating the relative variability of the ACI results. The 0 cm configuration had a systematically lower fine particle fraction as compared to the FPF_{ACI} (as well as the extended configurations). The fine particle fraction for the 0 cm configuration was statistically different (ANOVA, $p<0.05$) than those tested with the ACI for six of the seven formulations tested (the seventh had a $p=0.068$) and the correlation coefficient was 0.815 ($R^2=0.94$). Correlation coefficients for the 20 and 40 cm extension were higher compared to the ACI, having correlation coefficients of 0.93 ($R^2=0.92$) and 0.98 ($R^2=0.96$), respectively. It was speculated that the particles flowing through the TSI system still contained ethanol by the time they reached the impactor plate (inadequate drying time); this will be discussed in the next section.

Residual Ethanol Testing

To evaluate if unevaporated ethanol remained in the aerosol droplets as they passed the impactor plate, ethanol sensitive paper was fitted over the impactor plate, and inhalers containing four different concentrations of ethanol (5, 10, 15, and 20% w/w, 0.08% w/w BDP) were tested. These qualitative results can be seen in Fig. 5, where the dark markings indicate aerosol droplets containing ethanol have impacted onto the plate. The lightly colored area in the middle of some of these markings is attributed to a very high concentration of ethanol that saturates the indicator paper in that area as well as residual drug from the formulation. Aerosol particles impacting onto the plate while tested with the 20 or 40 cm extension appear to contain lower amounts of ethanol compared to the 0 cm configuration. In fact, the particles from the 5% ethanol formulation appeared to be completely dry with the 40 cm extension. Since the ethanol sensitive paper test is not quantitative, it does not indicate which extended length will be most appropriate, however, the results do suggest that evaporation is an important consideration when evaluating extension length. The observed paper results support the difference in the percent fine particle mass between the 0 cm and the 20 and 40 cm extensions relative to the ACI. The increased drying time prior to the single stage impactor plate of the TSI system appears necessary in order to correlate to the ACI.

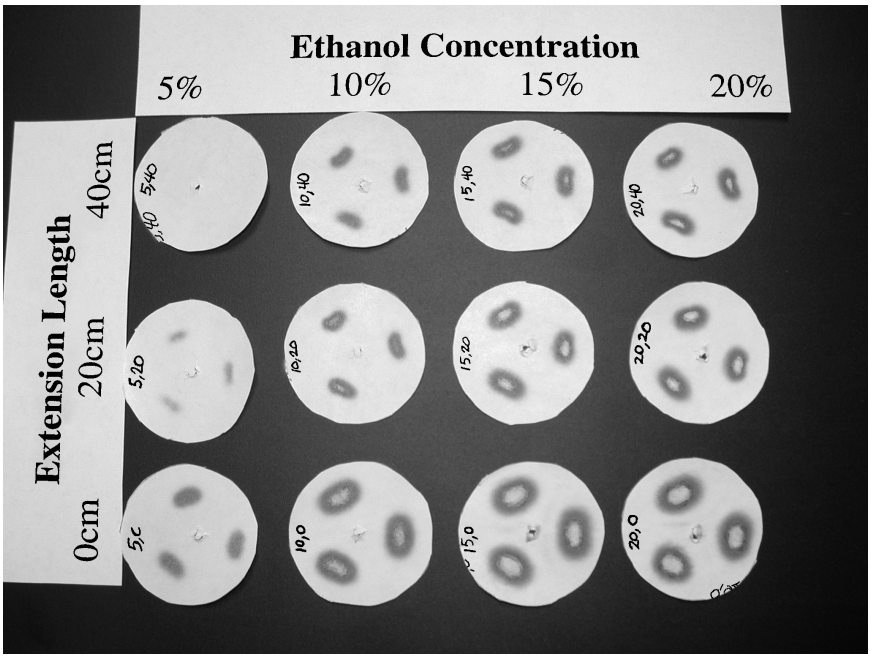

FIGURE 5 Ethanol Sensitive Paper was Fitted Over the Impactor Plate on the TSI System to Determine if Ethanol Remained in Aerosol Particles as They Passed. The Dark Markings on the Paper Indicate Presence of Ethanol.

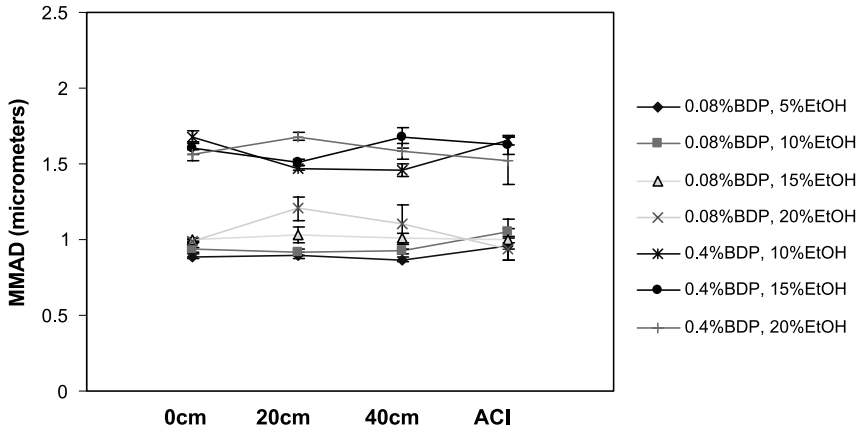

FIGURE 6 **Mass Median Aerodynamic Particle Size (MMAD) for Each TSI Configuration as well as for the Andersen Cascade Impactor (ACI).**

Particle Size

As shown in Fig. 6, particle size (mass median aerodynamic diameter, MMAD) was not affected by a change in inlet extension length for any TSI configuration (0, 20, and 40 cm). The fact that the particle size does not change with increasing extension length supports the supposition of a dried aerosol. Aerosol droplets in the TSI system mix with additional carrier air as they continue on the path to the APS, affording adequate time for ethanol to evaporate before size characterization. As a result, the particle size may be considered to be the residual (or dry) particle size which is predominately affected by drug concentration (non-volatile). In addition, even though the theoretical methodology for obtaining particle size data for the ACI and TSI 3320 are different, the numerical MMAD values are in very good agreement.

Product Performance of Ethanol/HFA 227 Solution Formulations

While the focus of this study was to evaluate two different instruments for characterizing pMDI, the results revealed an important relationship between USP inlet deposition and fine particle mass and the concentration of ethanol in the formulation, also discussed by Smyth (2003). From the summation of the data generated, increasing concentrations of ethanol had an inverse effect on FPF. For the TSI system, FPF is defined as the fine particle mass

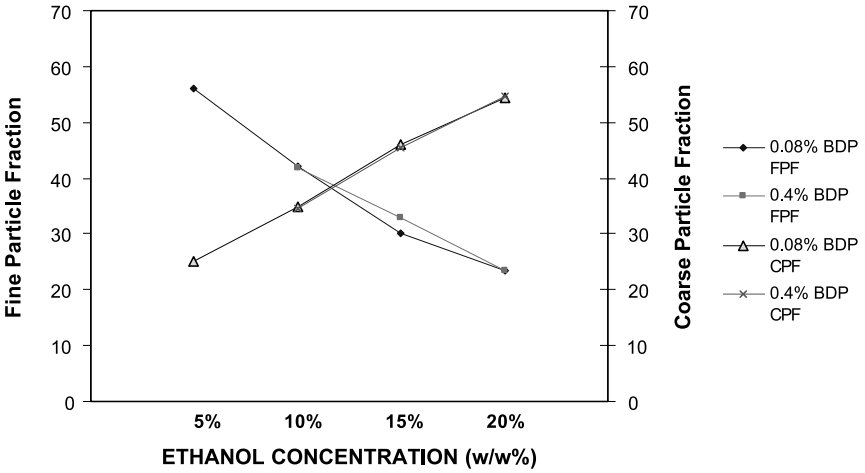

FIGURE 7 **Average Fine Particle Fraction (FPF) and Coarse Particle Fraction (CPF) as a Function of Ethanol Concentration.**

(aerodynamic mass <4.7 μm) divided by the sum of the masses collected from the USP inlet, impactor plate, and filter. The numerator in this equation represents the amount of drug that can reach target tissue in the lung; the denominator represents the total amount of drug the subject is exposed to (not the total amount actuated). Coarse particle fraction (CPF)=1-FPF; also stated, it is the amount of drug >4.7 μm delivered ex-actuator (i.e., amounts collected from the USP inlet and impactor plate divided by the sum of the amounts collected from the inlet, impactor plate, and filter). For the ACI, similar calculation were done, particles <4.7 μm are stage 3 through the filter and >4.7 μm are again the USP inlet and stages 0–2 as described above. Figure 7 graphically depicts the relationship between ethanol concentration, FPF, and CPF. It is clear that as ethanol concentration increases there is a significant decrease in FPF and a corresponding increase in CPF. Others (Gupta et al., 2003; Myrdal et al., 2004a, 2004b; Steckel & Müller, 1998) cite similar results using solution pMDIs, demonstrating that increasing amounts of ethanol in a given formulation can adversely affect product performance. These studies utilized 134a propellant based systems with ethanol as a cosolvent. Gupta and coworkers (2003) demonstrated that ethanol can act as an effective solubilizer for BDP; however, they found that the gain in solubility is offset by the decrease in FPF. In fact, as ethanol concentrations exceeded 10% w/w, the efficiency of the system started to plateau and no further gain in fine particle mass was realized, even though solubility continued to increase.

CONCLUSION

The process of characterizing an aerosol produced from a pMDI can be a challenging endeavor, especially for those formulations that contain semi-volatile excipients, such as ethanol used in this study. While the ACI has traditionally been viewed as a standard in aerosol characterization, the operator time and effort needed for testing is intensive. The TSI 3306/3320 system has been presented as an alternative instrument to more efficiently evaluate pharmaceutical aerosol products. However, in order to utilize the TSI system as a surrogate for the ACI instrument, it is necessary to sample these dynamic aerosols via the single stage impactor at approximately the time frame during the evaporation process. The current study confirms that an additional vertical extension must be incorporated with the USP inlet extension of the Model 3306, in order to obtain quantitative results that closely match those measured by the ACI. Specifically, those formulations containing 10–20% w/w ethanol will need a 20–40 cm vertical extension in order to obtain FPF that are similar to those obtained from ACI analysis.

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