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# Aiming for a moving target: Challenges with impactor measurements of MDI aerosols

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**Abstract**

Experiments were conducted to illustrate some of the challenges associated with measuring dynamic MDI aerosols. Experimental HFA-134a solution MDIs containing 8 or 20% ethanol were measured using the Andersen cascade impactor using three different inlets. It was demonstrated that the size distribution of MDI aerosols changes substantially during the measurement process. The measured size distribution was shown to be dependent on the degree of evaporation that has occurred prior to size measurement. Additionally, the degree of evaporation prior to measurement also influences the number of modes present in the measured size distribution. While MDI aerosols appeared to have a separate large particle mode when measured using the U.S. Pharmacopeial induction port ("USP inlet"; [U.S. Pharmacopeia, 1996. Physical tests and determinations <601> aerosols, metered dose inhalers, and dry powders. Pharmacopeial Forum 22, pp. 3065–3095]), the aerosols were shown to be monomodal when measured using a large volume inlet. The apparent large particle mode observed with the USP inlet seem rather to be droplets from the same monomodal distribution that have not fully evaporated. The complex interaction of the MDI plume and inlet configuration was described. Inlet design was shown to influence inlet deposition, measured particle size, and even deposition in the actuator mouthpiece. Inlet deposition was shown to be highly size-dependent with large droplets being collected more efficiently than smaller droplets.


*Keywords:* Cascade impactor testing; Aerodynamic particle size; Variability; Evaporation

## 1. Introduction

Aerodynamic particle size distribution measurements are widely used to characterize the aerosols from metered dose inhalers (MDIs) since deposition in the respiratory tract has been previously shown to be a function of aerodynamic particle diameter (Morrow, 1966; Howarth, 2001; Harrison et al., 1997; Hickey et al., 1996). Typically, aerodynamic particle size distribution measurements are done using cascade impactors (CIs). A thorough evaluation of CI measurement of MDI aerosols is provided elsewhere (Mitchell and Nagel, 2003). CIs are simple, inexpensive, and robust instruments for measuring aerodynamic size distributions and are widely used for characterizing aerosols in other fields as well (Marple, 2004). The most widely used CI for characterizing pharmaceutical aerosols is the Andersen Mark-II Cascade Impactor ("ACI", Thermo-Andersen, Smyrna, GA). In recent years, a number of additional impactors have been used extensively for characterizing pharmaceutical aerosols. Examples include the Next Generation Pharmaceutical Impactor ("NGI", MSP Corporation, Shoreview, MN), Marple-Miller Impactor (MSP Corporation, Shoreview, MN), and Multi-Stage Liquid Impinger ("MSLI", Copley Scientific, Nottingham, UK).

There are many potential sources of variability when making CI size distribution measurements (see for example, Christopher et al., 2003; Mitchell and Nagel, 2003). Despite these measurement challenges, CIs have been widely used since the 1940s (May, 1945) and are capable of generating consistent size distribution measurements. This is particularly true for environmental aerosols that are relatively static during the measurement process. However, CI measurements of dynamic aerosols, such as MDI aerosols, present challenges. During CI testing, the MDI aerosol changes from atomized droplets to residual particles. The atomized droplets contain propellant, drug (dissolved or suspended as fine particles), often a cosolvent (e.g. ethanol), and possibly a non-volatile excipient or surfactant. The residual particles contain drug and any non-volatiles in the formulation

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and are typically about an order of magnitude smaller than the atomized droplets (Stein and Myrdal, 2004). Thus, the nature of the aerosol changes significantly during the measurement process. What is measured is very much a function of how and when in the process the aerosol is measured. Much of the change of the aerosol occurs as it passes through the actuator mouthpiece and inlet, but droplet evaporation can continue even as the aerosol passes through the upper stages of the ACI (Myrdal et al., 2004). Due to the fact that the aerosol is changing during the measurement process, MDI size distribution measurements are highly sensitive to the testing apparatus used.

Depending on the configuration of the test apparatus, the MDI aerosol may be at a different point in the evaporation process during measurement resulting in differences in the measured size distribution depending on the equipment used (Stein et al., 2000; Myrdal et al., 2006). This has been observed in previous studies comparing size distribution measurements obtained using the ACI and the Model 3306 Impactor Inlet coupled to the Model 3321 Aerodynamic Particle Sizer Spectrometer (TSI Inc., Shoreview, MN; Stein et al., 2000; Myrdal et al., 2004, 2006). In these studies, the mass of particles with aerodynamic diameters larger than 4.7 μm was shown to be consistently higher for measurements made with the 3306 Impactor Inlet compared to those measured using the ACI (both setups have an impactor stage with a 4.7 μm cutpoint). This has been attributed to the differences in the time required for the droplets to reach the 4.7 μm cutpoint impactor stage (the only stage in the Model 3306; Stage 2 in the ACI) for the two test setups (Myrdal et al., 2004). Indeed, heated extensions to the USP inlet (United States Pharmacopeia, 1996) have even been used in order to obtain equivalence between size distributions measured with the ACI and Impactor Inlet (Myrdal et al., 2006). These results demonstrate that subtle differences in testing conditions, such as changes in flow path of the aerosol prior to measurement, influence MDI size distribution measurements.

Environmental factors, such as the temperature and relative humidity, can also influence MDI size distribution measurements. For example, it has been shown that MDI aerosol size distributions are altered when measured at temperatures above about 35 °C and relative humidities above about 95% (Lange and Finlay, 2000; Mitchell et al., 2003). This is likely due to changes in the droplet evaporation caused by interaction of water vapor with the surface of the evaporating droplets (Lange and Finlay, 2000). While this is important for mechanical ventilation applications, previous results (Lange and Finlay, 2000) imply that temperature and relative humidity are likely to have minimal impact on the MDI size distributions in this study or during typical quality control testing. On the other hand, measurements of aqueous nebulizer aerosols have been shown to be highly sensitive to environmental conditions (Finlay and Stapleton, 1999; Jauernig et al., 2004). In order to obtain consistent CI data from nebulizers, it is common to control the temperature and relative humidity of the air entering the testing apparatus—in some cases by using air saturated with water vapor (Finlay and Stapleton, 1999) or by refrigerating the impactor equipment (Berg and Asking, 2004). While the influence of evaporation on the measurement of nebulizer aerosols and MDI aerosols delivered in mechanical ventilators has been studied, much less is known about the influence of evaporation on typical size distribution measurements of MDIs.

The objective of this paper is to illustrate some of challenges associated with measuring dynamic MDI aerosols. This will be done by comparing size distributions measured with the ACI using various inlet configurations. It will be demonstrated that MDI aerosols change during the ACI measurement and that, as a result, the measured size distribution is highly sensitive to the inlet design.

## 2. Materials and methods

Aerodynamic particle size distribution measurements were made on two different experimental MDI configurations using the ACI. The MDI configurations tested contained approximately 0.167% (w/w) beclomethasone dipropionate, 8 or 20% (w/w) ethanol, and HFA-134a as the remainder of the formulation. The MDIs used 50 mcl Spraymiser™ valves and QVAR® actuators with orifice diameters of approximately 0.3 mm.

ACI tests were conducted by coupling the MDI to the test inlet and actuating the MDI five times while waiting approximately 10 s between each actuation. The flowrate through the ACI setup was set at 28.3 ± 0.5 lpm for all tests reported in this paper. The amount of drug deposited on the valve, actuator, and various components of the ACI apparatus was determined by rinsing each component with a known volume of methanol and analyzing the rinse solution with a previously described HPLC method (Stein and Olson, 1997). In addition to assaying the drug on the ACI impaction plates and filter, the drug deposited on stage 0 ("jet stage 0") was also assayed since a small amount of drug collects on this stage during testing. Both MDI formulations were tested using each of the three inlet configurations listed below. Five replicate measurements (each using a different MDI canister and actuator) were made for each MDI/inlet combination. The temperature and relative humidity was monitored during testing and was between 20 and 25 °C and between 30 and 60%, respectively, for all tests.

The three inlet configurations used were: (1) the USP inlet; (2) the USP inlet with a 20 cm extension to the vertical section of the inlet (see Myrdal et al., 2004 for details); and (3) the approximately 20 l inlet accessory (Model 3242 AeroDryer™ accessory; "large volume chamber") that was previously sold for use with the Aerosizer® Mach II Particle Size Analyzer (TSI, Inc., Shoreview, MN). The inlets used were selected based on their relevance to CI tests done for quality control purposes by companies that develop and manufacture MDI products. The USP inlet, while having limited anatomical relevance, was selected since it is the most widely used inlet for CI testing of MDIs. The other inlets used were selected due to the fact that they provide varying amounts of time for the MDI aerosol to evaporate prior to measurement in the CI. This is particularly true for the large volume chamber. There are many other inlets that have been used in CI testing of MDIs (see for example Dolovich and Rhem, 1998; Naini et al., 2004; Van Oort et al., 1994). Some inlets with increased anatomical relevance have been developed for CI testing (e.g.

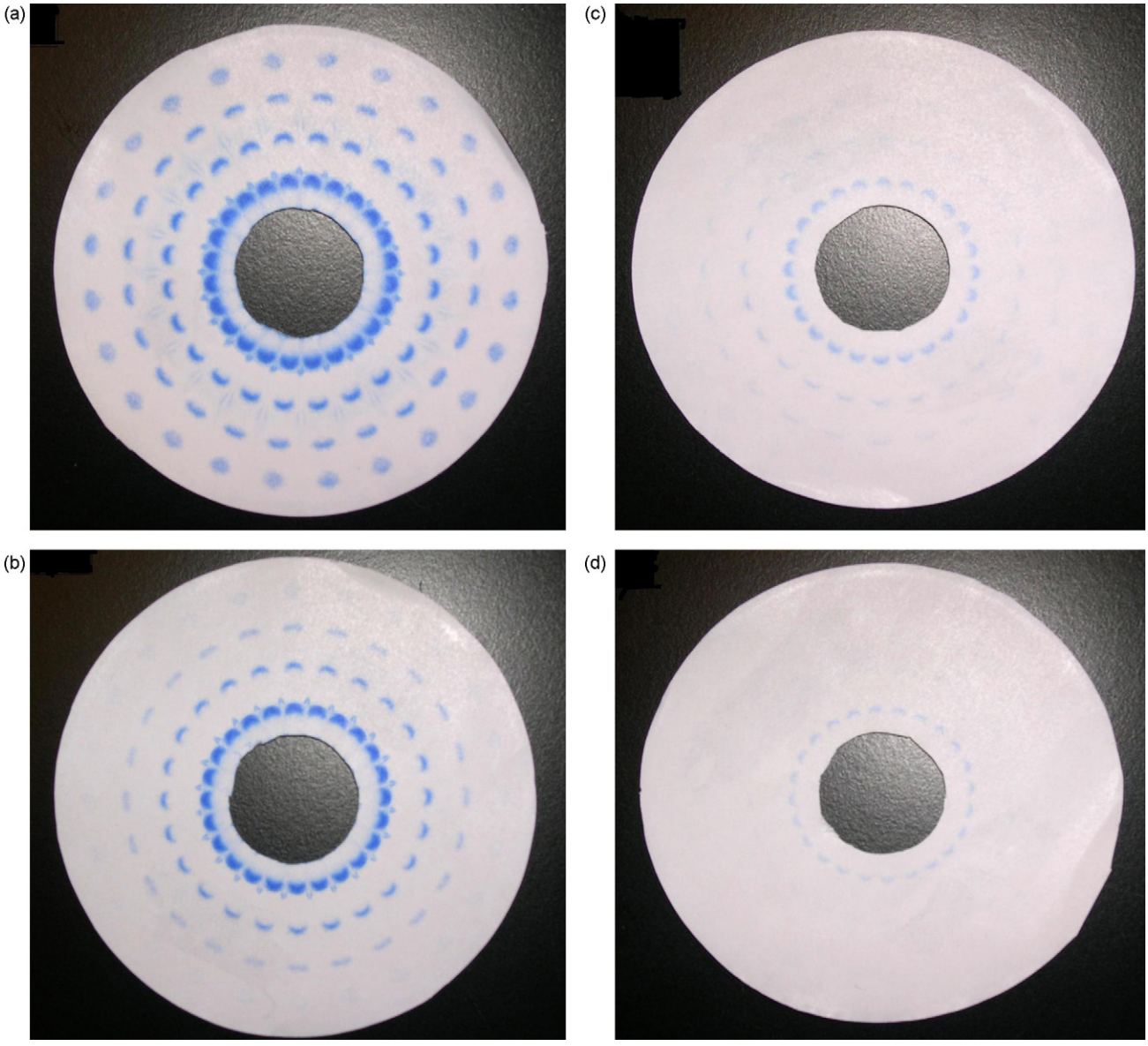


Fig. 1. (a) Pictures of ethanol-sensitive paper recovered from Plate 0 of the ACI after testing of MDIs with 20% ethanol using the standard USP inlet. (b) Pictures of ethanol-sensitive paper recovered from Plate 0 of the ACI after testing of MDIs with 20% ethanol using the USP inlet and the 20 cm inlet extension. (c) Pictures of ethanol-sensitive paper recovered from Plate 0 of the ACI after testing of MDIs with 8% ethanol using the standard USP inlet. (d) Pictures of ethanol-sensitive paper recovered from Plate 0 of the ACI after testing of MDIs with 8% ethanol using the USP inlet and the 20 cm inlet extension.

Dolovich and Rhem, 1998; Zhang et al., 2004). However, these inlets were not used since the focus of this investigation was on understanding factors relevant to typical CI tests done for quality control purposes rather than simulating actual in vivo effects.

Drug deposition in the vertical extension of the USP inlet was not measured since previous investigations have indicated that the amount is negligible (Myrdal et al., 2004). Drug deposition in the large volume chamber was not measured because it had previously been determined that approximately 5% of the drug deposits in this chamber (Stein and Myrdal, 2004). The aerodynamic particle size distribution was calculated from the amount of drug deposited on the various plates of the ACI using DistFit$^{TM}$ fitting software (Chimera Technologies, Inc., Forest Lake, MN). For most of the experiments, the size distribution was assumed to be a monomodal lognormal distribution. However, for some of the experiments this assumption was problematic due to a surprisingly high amount of deposition on Plates 0 and 1 of the ACI. For calculation of the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the MDI aerosols, the drug mass on Plates 0 and 1 was therefore ignored as it did not fit with the rest of the distribution. This will be discussed in detail in Section 3.

ACI tests were also conducted using modified collection surfaces to assess ethanol deposition on the impactor plates. The plates were covered with ethanol-sensitive paper and were visually inspected to qualitatively assess the amount of ethanol remaining in the droplets when collected on the ACI impaction plates. For these experiments, ethanol-sensitive paper was placed on the various impaction plates of the ACI using an

Table 1
A summary of results from ACI testing of two different MDI formulations using three different inlet designs

| | 8% Ethanol MDIs | | | 20% Ethanol MDIs | | |
|---|---|---|---|---|---|---|
| | USP inlet | USP inlet + 20 cm extension | Large volume chamber | USP inlet | USP inlet + 20 cm extension | Large volume chamber |
| Valve stem | 0.9 | 1.0 | 0.9 | 0.8 | 0.8 | 0.8 |
| Actuator | 28.8 | 27.5 | 20.6 | 25.3 | 23.9 | 15.0 |
| USP inlet | 24.4 | 25.8 | N/A | 44.7 | 44.7 | N/A |
| Stage 0 | 0.2 | 0.2 | 0.3 | 0.5 | 0.5 | 0.2 |
| Plate 0 | 0.5 | 0.5 | 0.3 | 1.4 | 1.1 | 0.2 |
| Plate 1 | 0.3 | 0.3 | 0.4 | 0.4 | 0.4 | 0.4 |
| Plate 2 | 0.2 | 0.2 | 0.5 | 0.1 | 0.1 | 0.8 |
| Plate 3 | 0.7 | 0.7 | 1.6 | 0.6 | 0.7 | 4.1 |
| Plate 4 | 4.0 | 4.4 | 8.0 | 2.6 | 2.6 | 16.8 |
| Plate 5 | 17.1 | 17.5 | 30.2 | 8.0 | 7.7 | 29.4 |
| Plate 6 | 11.2 | 10.9 | 16.3 | 4.3 | 4.3 | 10.0 |
| Plate 7 | 5.9 | 5.6 | 8.3 | 2.2 | 2.2 | 4.0 |
| Filter | 6.2 | 5.9 | 7.0 | 2.5 | 3.2 | 5.1 |
| Total | 100.3 | 100.4 | 94.3 | 93.3 | 92.2 | 86.8 |
| Total in impactor | 46.2 | 46.2 | 72.8 | 22.5 | 22.9 | 71.1 |

Each value represents the average amount of drug, in mcg/actuation, from five test results.

adhesive. The ethanol-sensitive paper was gently rubbed in order to ensure that the surface was lying flat and that there had been minimal change in the distance from the impactor nozzle to the collection surface. This testing was done with the same two MDI formulations and using the same three inlet configurations listed above.

## 3. Results and discussion

### *3.1. The dynamic nature of MDI aerosols during the ACI measurement process*

CI testing of MDIs with 8 and 20% ethanol were done using standard impaction plates and plates covered with ethanol-sensitive paper. These experiments were then analyzed to provide insight into the degree of droplet evaporation that occurs in the CI during testing.

#### *3.1.1. Deposition on the ACI impaction plates—ethanol-sensitive paper*

Tests with the ethanol-sensitive paper were conducted using the three inlet configurations previously described. Fig. 1 shows pictures after testing of the ethanol-sensitive paper that was placed on Plate 0 for the tests with the USP inlet and the USP inlet with the 20 cm extension. Pictures were not included for the tests using the large volume chamber inlet since no evidence of ethanol deposition could be seen for either formulation with this inlet. When the USP inlet was used for the measurement of the 20% ethanol MDIs there was a substantial amount of ethanol deposition on Plates 0 and 1. There was no evidence of ethanol deposition on any of the other plates. When the USP inlet was used for the measurement of the MDIs with 8% ethanol, a lesser amount of ethanol deposition was observed on Plates 0 and 1 and no deposition was observed for any other plates. The large difference in the amount of ethanol deposition on Plates 0 and 1 between the two formulations is due to the fact that droplets from the MDIs with 8% ethanol evaporate more rapidly than those from the MDIs with 20% ethanol (Stein and Myrdal, 2006) and thus are dryer by the time they reached the stages of the ACI.

When the 20 cm USP inlet extensions was used, the amount of ethanol deposition on Plates 0 and 1 was noticeably lower for both of the MDI formulations. This indicates the 20 cm extension allowed for further evaporation of the droplets prior to collection on Plate 0. When the large volume chamber was used, no ethanol deposition was observed using the ethanol-sensitive paper on any of the plates—even for the formulation with 20% ethanol. This indicates that the large volume chamber provided sufficient time for complete droplet evaporation to occur prior to the impactor size distribution measurement.

#### *3.1.2. Deposition on the ACI impaction plates—HPLC analysis*

The size distribution measurements determined from HPLC analysis of the ACI plates are summarized in Table 1 for the various test configurations. The data in Table 1 represent the average amount of drug (in mcg/actuation) from five measurements. The amount of drug collected in the USP inlet was much higher for the MDIs with the lower ethanol level. This has been reported elsewhere (Meakin et al., 2000; Stein and Stefely, 2003; Gupta et al., 2003). The MDIs with 20% ethanol had less total drug recovered due to the decreased formulation density and the resulting decrease in shot weight for these MDIs. By comparing the total drug recovered from the tests using the USP inlet with and without the 20 cm extension, it was confirmed that drug deposited in the vertical extension for both of the formulations was minimal. The amount of drug deposited in the large volume chamber was estimated by comparing the total amount of drug recovered from the tests using the chamber to those recovered from the other two configurations. The amount of drug lost in the chamber was estimated to be about 6%. It has been previously

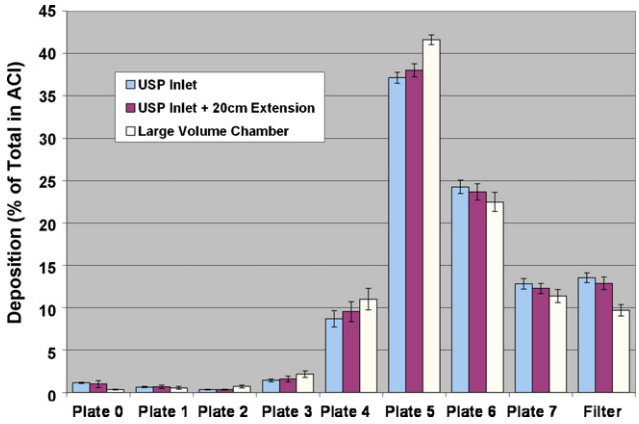


Fig. 2. Deposition of drug on the various stages of the ACI from testing of MDIs with 8% ethanol using three different inlet configurations. The deposition is normalized as a percent of the total amount measured in the impactor.

estimated that about 5% of the drug deposits in the chamber during testing (Stein and Myrdal, 2004).

Deposition in the ACI from the testing of the MDIs with 8 and 20% ethanol using the various inlets are summarized in Figs. 2 and 3, respectively. The drug deposition on each plate is analyzed in Figs. 2 and 3 as a percent of the total amount of drug entering the impactor. For the tests using the USP inlet, the amount of drug depositing on Plates 0 and 1 of the ACI was higher than would be expected if the aerosol followed a lognormal size distribution. This was particularly true for the MDIs with 20% ethanol. The drug deposition on these plates was likely associated with droplets that still contained ethanol as they entered into the ACI. This is consistent with the findings from when the ethanol-sensitive paper was used. However, when the large volume chamber was used the amount of drug collecting on Plates 0 and 1 was much closer to what would be expected for a truly lognormal aerosol.

The difference in the deposition on the top two plates was particularly striking for the formulation with 20% ethanol (Fig. 3). When the large volume chamber was used, less than 1% of the drug entering into the impactor collected on Plates 0 and 1 compared to 8% when the USP inlet was used and 7% when the 20 cm USP inlet extensions was used. The deposition observed on Plates 0 and 1 appear to be the result of droplets that have not fully evaporated.

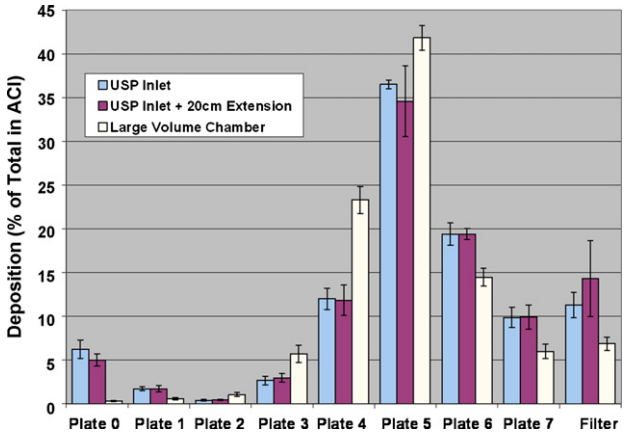


Fig. 3. Deposition of drug on the various stages of the ACI from testing of MDIs with 20% ethanol using three different inlet configurations. The deposition is normalized as a percent of the total amount measured in the impactor.

One potential objection to the above explanation of the difference in the deposition on Plate 0 and 1 among the three inlets (Fig. 3) is that the particles that would have collected on Plates 0 and 1 are the portion of the aerosol (i.e. the 6% described earlier) that deposits in the large volume chamber during testing. However, this explanation does not fit with the data from the MDIs with 8% ethanol content since the deposition in the large volume chamber significantly exceeds the deposition on Plates 0 and 1 for any of the tests. Additionally, this objection is not satisfactory since it is highly unlikely that large droplets would deposit in the large volume chamber and yet penetrate through the USP inlet (see Section 3.2.4 where it is shown that large droplets are far less likely to deposit in the large volume chamber than in the USP inlet). Thus, the best explanation for the deposition observed on Plates 0 and 1 is that it is due to droplets than have not fully evaporated.

### *3.1.3. Are MDI aerosols bimodal?*

Previous investigators (Smyth and Hickey, 2003) have observed a bimodal nature of aerosols from HFA-134a solution MDIs similar to those tested in this paper. In particular, a small particle mode with a median particle size of approximately 1 μm and another large particle mode with a median particle size of at least 10 μm were observed from both ACI measurements and laser diffraction (LD) measurements. Smyth and Hickey measured HFA-134a MDIs with ethanol concentrations of 2.5, 10, 20, and 50% (w/w) and observed a substantial amount of drug deposition on Plate 0 of the ACI, particularly for formulations with ethanol concentrations of at least 10%. They concluded from these results, and LD measurements on the same aerosol, that MDI aerosols are bimodal in nature and that the deposition on the top plates was associated with a distinct large particle mode. It should be noted that LD measurements of MDI aerosols are problematic due to complex changes in the index of refraction of the gas in the measurement volume as evaporating propellant mixes with air. This can lead to an effect known as "beam steering" which sometimes produces spurious large particle measurements. However, Smyth and Hickey demonstrated in a compelling manner that the large droplet mode they observed was not due to beam steering effects (Smyth and Hickey, 2003).

The test results reported in this paper may shed light into the very similar results reported by Smyth and Hickey (2003). The comparison of size distribution measurements made using the USP inlet and those made using the large volume chamber seem to indicate that the deposition on Plate 0 is due to deposition of droplets that have not yet evaporated to their residual size rather than due to a distinct large particle mode. The measurements made using ethanol-sensitive paper on the impaction surfaces seem to confirm this since the ethanol deposition on the top plates of the impactor was eliminated when the large volume chamber was used. The fact that only a single mode was observed when the large volume chamber was used with

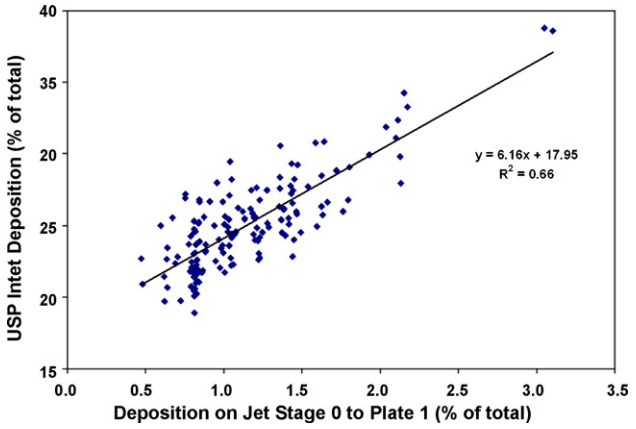


Fig. 4. The relationship between deposition of drug on the jet stage 0, Plate 0, and Plate 1 of the ACI and the deposition in the USP inlet from ACI testing of MDIs with 8% ethanol and 0.083% beclomethasone dipropionate.

the ACI indicates that MDI aerosols are not aerosolized into two distinct modes during atomization. An alternative hypothesize is that the bimodal nature of the MDI aerosols observed by Smyth and Hickey (2003) is due to the manner in which the aerosol was measured—namely, the small particle mode was associated with droplets that had fully evaporated and the large particle mode was associated with droplets that had not yet fully evaporated and would have eventually been included in the same small particle mode after complete evaporation.

### *3.1.4. The relationship between ethanol deposition and the overall ACI size distribution profile*

Figs. 1–3 illustrate how MDI size distribution measurements are influenced by the degree to which the droplets have fully evaporated prior to entering into the ACI. It has previously been demonstrated that inlet deposition during MDI testing is highly correlated to the time required for evaporation of the atomized MDI droplets (Stein and Myrdal, 2006). In that investigation, it was shown that lower volatility formulations require more time for the droplets to evaporate and therefore have increased USP inlet deposition. This was observed in this study as well. The MDIs with 20% ethanol had much higher USP inlet deposition than the MDIs with only 8% ethanol (Table 1). As mentioned previously, the aerosol from the 20% ethanol MDIs also had much more residual ethanol in the droplets as they were measured in the ACI. Such a trend among different formulations is not surprising. Namely, the formulations that had less complete evaporation of the aerosol prior to its entry into the ACI also had increased inlet deposition. However, it is surprising that a similar trend was observed even for MDIs of the identical formulation. Fig. 4 shows a compilation of numerous studies (Stein, 1999; Stein et al., 2002, 2003; and other unpublished studies with identical test procedures) conducted using MDIs that are identical to the 8% ethanol formulation MDIs used above except that the BDP concentration was approximately 0.083% (w/w). There was a correlation between USP inlet deposition and deposition of droplets with 'residual ethanol' on the top plates of the ACI. While the correlation was modest ($r^2 = 0.66$), the relationship was highly statistically significant ($p$-value < 0.001) as determined by a linear regression analysis. Despite constituting a very small portion of the overall aerosol mass, the drug on the top two plates was predictive of the overall ACI test results for this MDI formulation. In general, the tests with higher USP inlet deposition also had higher than average deposition on the top plates indicating that the droplets had evaporated to a lesser degree.

There are many testing factors that could potentially lead to differences in the evaporation rate during testing (formulation composition, environmental conditions, the initial temperature of the formulation, changes in the initial size of the atomized droplets, etc.—see for example, Finlay and Stapleton, 1999; Stein and Myrdal, 2006). However, all of the tests in Fig. 4 used identical MDI configurations and test methods. The source of the subtle changes in the degree of evaporation of the droplets prior to entering the ACI is not known. Nevertheless, it is interesting that these subtle differences in evaporation can lead to large differences in the USP inlet deposition and ACI profile.

The previous discussion illustrates the inherent challenges associated with size measurement of dynamic MDI aerosols. MDI aerosols are changing even as they are measured during CI testing. MDI particle size distributions inherently change as the volatile and semi-volatile components of the formulation evaporate. While most of the evaporation (and change in size distribution) occurs in the inlet, some even occurs in the CI itself. Since the aerosol is changing during the measurement process (both in the inlet and in the ACI itself), we are effectively 'aiming for a moving target' and ought not be surprised by a fair degree of method variability.

## *3.2. The complex interaction of the MDI aerosol and the inlet*

As discussed in the previous section, MDI aerosols are changing even as they are measured during CI testing. The aerosols are particularly dynamic as they travel through the inlet portion of the CI where the droplets rapidly decelerate from very high velocities (30–60 m/s; Clark, 1991) down to the steady-state velocity of the airflow in the inlet. Additionally, much of the evaporation occurs in the inlet and the droplets are rapidly changing in size. Not surprisingly, CI test results are highly dependent on the inlet selected. In this section, the ACI tests summarized in Table 1were analyzed to illustrate the complex interaction between the MDI aerosol and the inlet.

### *3.2.1. The influence of inlet design on mass of drug reaching impactor*

The tests results in Table 1 indicate that the amount of drug reaching the ACI was much higher when the large volume chamber was used compared to when the USP inlet was used. This is not surprising since the chamber allows time for the droplets to decrease in both size and velocity prior to approaching potential collection surfaces. The amount of drug reaching the ACI increased by more than 50% when the large volume chamber was used with the MDIs containing 8% ethanol. The increased amount reaching the ACI was particularly striking for the 20% ethanol formulations where the use of the large volume chamber

resulted in more than a three-fold increase in drug entering into the ACI. This is due to the fact that formulations with higher ethanol levels have a high degree of USP inlet deposition. Thus when the large volume chamber is used (and inlet deposition is minimized) the change in the amount of drug reaching the ACI is dramatic.

### 3.2.2. The influence of inlet design on mouthpiece deposition

A particularly surprising aspect of the data in Table 1 is the fact that MDI actuator mouthpiece deposition was influenced significantly by the selection of the inlet. Mouthpiece deposition was substantially lower for the tests conducted using the large volume chamber as opposed to those using the USP inlet (with or without the extension). These differences were statistically significant ($p$-value < 0.001 for the 20% ethanol MDIs, $p$-value = 0.002 for the 8% ethanol MDIs).

The source of the differences in actuator deposition is not currently understood. One hypothesis is that when the large volume chamber was used, the MDI plume was able to expand without restriction whereas the plume expansion was restricted when the USP inlet was used resulting in different flow dynamics and therefore different deposition profiles. It is possible that the unrestricted plume expansion resulted in less turbulence within the actuator mouthpiece, leading to reduced mouthpiece deposition when the large volume chamber was used. When an MDI is actuated, the rapid evaporation of propellant and cosolvent briefly influences the flowrate through the test apparatus. A brief analysis may shed light into this. Suppose that 50 mcl of formulation is atomized in approximately 280 ms, the approximate duration of plume for the 8% ethanol MDIs (Gabrio et al., 1999). If the HFA-134a is assumed to completely evaporate during the 280 ms atomization event, this will result in approximately 12 ml of HFA-134a vapor being added to the system. While 12 ml of vapor added to the system seems negligible, the burst of vapor is equivalent to a vapor flow of 3 lpm through the duration of the plume. The exact dynamics of the airflow through the system during MDI atomization are outside the scope of this paper. However, the brief calculation demonstrates that the evaporation of the HFA-134a during atomization may temporarily alter the flow dynamics in the system. It is possible that the influence that the burst of propellant vapor has on the flow dynamics in the system may be different for the various inlet designs. Further work is needed to understand the influence that the propellant vapor has on the flow dynamics in the CI test apparatus. While the reason for the differences in actuator mouthpiece deposition for the various inlet design is not yet understood, it illustrates the sensitivity of MDI size distribution measurements to the apparatus used—even mouthpiece deposition is influenced by the apparatus used!

### 3.2.3. Influence of inlet on measured mass median aerodynamic diameter

In addition to affecting the total amount of drug reaching the ACI during the size distribution measurements (Table 1), the inlet also influenced the size distribution of the drug reaching the ACI (Table 2). The size distributions measured using the large volume chamber had a substantially larger MMAD than those measured using the USP inlet (with and without the 20 cm extension). This is due to the fact that the larger atomized droplets tend to preferentially deposit in the USP inlet via turbulent deposition, thus biasing the measured size distribution towards smaller particle sizes (Naini et al., 2004; Stein and Myrdal, 2004; Stein and Gabrio, 2000). This size-dependent deposition in the USP inlet will be discussed in the following section. The difference in MMAD was larger for the 20% ethanol MDIs than for the 8% ethanol MDIs, probably since the 20% ethanol MDIs had much more USP inlet deposition.

Table 2
The MMAD calculated from the test results in Table 1 for MDIs with 8 and 20% ethanol tested using three different inlet configurations

| Inlet configuration | MMAD (μm) | |
|---|---|---|
| | 8% Ethanol | 20% Ethanol |
| USP inlet | 1.11 | 1.27 |
| USP inlet + 20cm extension | 1.15 | 1.21 |
| Large volume chamber | 1.26 | 1.70 |

### 3.2.4. Size-dependent deposition in the USP inlet

The measured size distributions from Table 1 were further analyzed to understand the size-dependent nature of the deposition in the USP inlet during ACI testing of MDIs. In order to do this, the amount of drug depositing on the plates of the ACI were compared for the tests using the USP inlet to those using the large volume chamber. By comparing the relative amount of drug on any given plate of the ACI for the two configurations, the size-dependent deposition in the USP inlet was investigated. Table 3 shows this information for the 20% ethanol MDIs. For example, Plate 5 of the ACI collects particles with residual aerodynamic diameters of about 1.1–2.1 μm. For the 20% ethanol formulation, residual particles in this range result from droplets with initial droplet diameters in the range of about 8.6–16.5 μm (Stein and Myrdal, 2004). Approximately 73% of the atomized droplets in this size range deposited in the USP inlet during ACI testing. The size-dependent collection characteristics of the USP

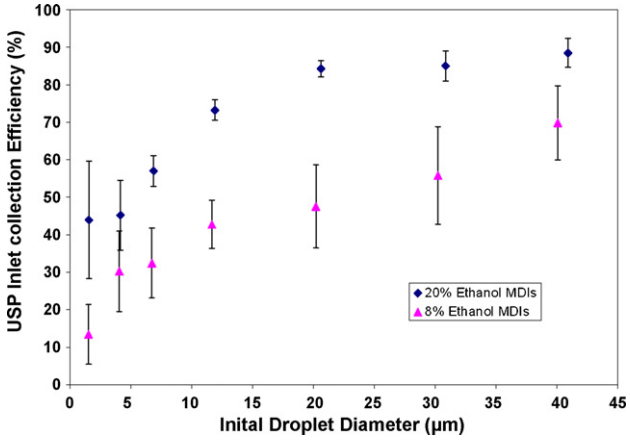


Fig. 5. The estimated efficiency with which the USP inlet collects MDI droplets of various atomized sizes.

Table 3
A summary of calculations estimating the collection of the USP inlet for droplets of varying size atomized from MDIs with 20% ethanol

| Impactor stage | ACI particle size range (μm)[a] | Range of initial droplets (μm)[b] | Median droplet size (μm)[c] | Average from USP inlet (μg/actuation)[d] | Large Volume chamber (μg/actuation)[e] | Collection efficiency (%)[f] |
|---|---|---|---|---|---|---|
| 2 | 4.7–5.8 | 36.8–45.5 | 40.9 | 0.09 | 0.78 | 88.5 |
| 3 | 3.3–4.7 | 25.9–36.8 | 30.9 | 0.62 | 4.15 | 85.0 |
| 4 | 2.1–3.3 | 16.5–25.9 | 20.6 | 2.64 | 16.77 | 84.2 |
| 5 | 1.1–2.1 | 8.6–16.5 | 11.9 | 7.89 | 29.44 | 73.2 |
| 6 | 0.7–1.1 | 5.5–8.6 | 6.9 | 4.30 | 10.00 | 57.0 |
| 7 | 0.4–0.7 | 3.1–5.5 | 4.1 | 2.19 | 4.00 | 45.2 |
| Filter | 0–0.4 | 0.8–3.1 | 1.6 | 2.85 | 5.08 | 43.9 |

[a] From "Operating manual for 1 ACFM Non-Viable Ambient Particle Sizing Sampler, Smyrna, Georgia"; Graseby-Andersen, Inc., 1985.
[b] Calculated using equations from Stein and Myrdal (2004) using "ACI Particle Size Range" as the residual particle size.
[c] Calculated as the square root of the product of the smallest and largest initial droplets in the size range (Hinds, 1999).
[d] Average from ACI tests using USP inlet with and without 20 cm extension in Table 1.
[e] Average from ACI tests using large volume chamber in Table 1.
[f] 100 × (1 − Average from USP inlet/Average from large volume chamber).

inlet are summarized in Fig. 5. It should be noted that the size of the droplets at the moment they deposited in the USP inlet could not be assessed since it would undoubtedly have changed between atomization and deposition. The collection efficiency could also have been represented as a function of the residual particle size as opposed to the initial droplet diameter. Analysis of the 8% ethanol MDI test results showed a similar trend to that of the 20% ethanol MDIs (Fig. 5). These findings are consistent with the hypothesis that large droplets are preferentially collected in the USP inlet via turbulent deposition (Stein and Gabrio, 2000; Stein and Myrdal, 2004).

## 4. Conclusions

Several challenges associated with CI measurement of dynamic MDI aerosols have been discussed. MDI aerosols undergo dramatic changes in particle size during CI measurements. As a result, MDI size distribution measurements are highly dependent on the way they are measured. The measured size distribution is dependent on the degree of evaporation of the volatile and semi-volatile components prior to measurement. Drug collected on the top plates of the ACI during size distribution measurements of two ethanol-containing MDI formulations was shown to be associated with droplets containing unevaporated ethanol. When the aerosol was allowed more time to evaporate prior to measurement, these large droplets were not present. As a result, a bimodal aerosol was observed when MDI aerosols were measured prior to complete evaporation of the volatile and semi-volatile components. While these larger droplets appear to be a separate mode when measured, it appears that they are actually droplets from the same monomodal distribution that have not fully evaporated. Thus, the way in which an MDI aerosol is measured not only influences parameters such as the MMAD and GSD, but also influences the number of modes measured in the distribution. The choice of inlet significantly influences the measured size distribution. This is due, in part, to the fact that the volume of the inlet influences the amount of time available for the aerosol to evaporate prior to measurement. The complex interaction of the MDI plume and the inlet even leads to significant changes of deposition in the MDI actuator mouthpiece when different inlets are used. Due to the dynamic nature of MDI aerosols and their complex interaction with the inlet and CI apparatus, a higher level of variability should be expected from CI testing of MDI aerosol compared to other aerosols commonly measured using CIs.

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