DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY®
Vol. 30, No. 8, pp. 859–868, 2004

# Comparison of the TSI Model 3306 Impactor Inlet with the Andersen Cascade Impactor: Solution Metered Dose Inhalers

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## ABSTRACT

The product performance of a series of solution Metered Dose Inhalers (MDIs) were evaluated using the TSI Model 3306 Impactor Inlet and the Andersen Cascade Impactor (ACI). The goal of the study was to test whether the fine particle and coarse particle depositions obtained using the Model 3306 were comparable to those results obtained by ACI testing. The analysis using the Model 3306 was performed as supplied by the manufacturer as well as with 20 cm and 40 cm vertical extensions that were inserted between the Model 3306 and the USP Inlet. Nine different solution formulations were evaluated. The drug concentrations ranged from 0.08 to 0.8% w/w and the ethanol cosolvent concentration varied between 5 and 20% w/w. In general, it was found that good correlations between the two instruments were obtained. However, for formulations containing 10–20% w/w ethanol it is shown that an extension fitted to the Model 3306 yielded an improved correlation to those obtained from the ACI.

*Key Words:* Metered dose inhaler; MDI; Andersen cascade impactor; Impactor inlet.

## INTRODUCTION

As part of the product performance testing of pharmaceutical aerosols such as MDIs, the aerodynamic particle size distribution and drug mass distribution is characterized. Traditionally this has been done using cascade impactors such as the Andersen Mark-II Cascade Impactor (Thermo-Andersen Inc., Smyrna, GA) or the Marple-Miller cascade impactor (MSP Corp., Minneapolis, MN). While the ACI is often

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DOI: 10.1081/DDC-200034575
0363-9045 (Print); 1520-5762 (Online)

considered the 'standard',[1] testing using the ACI (or any cascade impactor) is labor intensive. It would thus be valuable to have a method that would allow greater through-put for testing MDIs, especially at early stages of development. The Model 3306 provides a sampling arrangement similar to that of the ACI, since both utilize the same USP (U.S. Pharmacopeia) inlet. The notable difference is that the Model 3306 classifies the aerosol using a single stage impactor with a cutoff point of 4.7 μm aerodynamic diameter (at a flow of 28.3 L/min) instead of using multiple impaction stages. Figure 1 shows the flow schematic of Model 3306 Impactor Inlet. Chemical analysis of the Model 3306 allows for characterization of the 'coarse particle' drug mass (defined as particle mass with an aerodynamic diameter greater than 4.7 μm) as well as 'fine particle' drug mass (defined as mass with an aerodynamic diameter less than 4.7 μm). The coarse particle drug mass collects on the impaction plate, while the fine particle drug mass collects on a filter. The characterization of an aerosol spray into two fractions is not an entirely new testing concept. The twin impinger will also afford two defined aerosol fractions.[2] However, the Model 3306 offers the advantage of being integrated with the TSI Model 3321 Aerodynamic Particle Sizer (APS). Less than 1% of the aerosol penetrating through the USP inlet is sampled isokinetically and drawn into the APS for simultaneous particle size measurement.[3,4] The remainder of the aerosol passes through the single-stage impactor enabling chemical analysis characterization of the distribution of the drug substance.

The present study compares the mass distribution of solution MDIs obtained using the ACI, with the Model

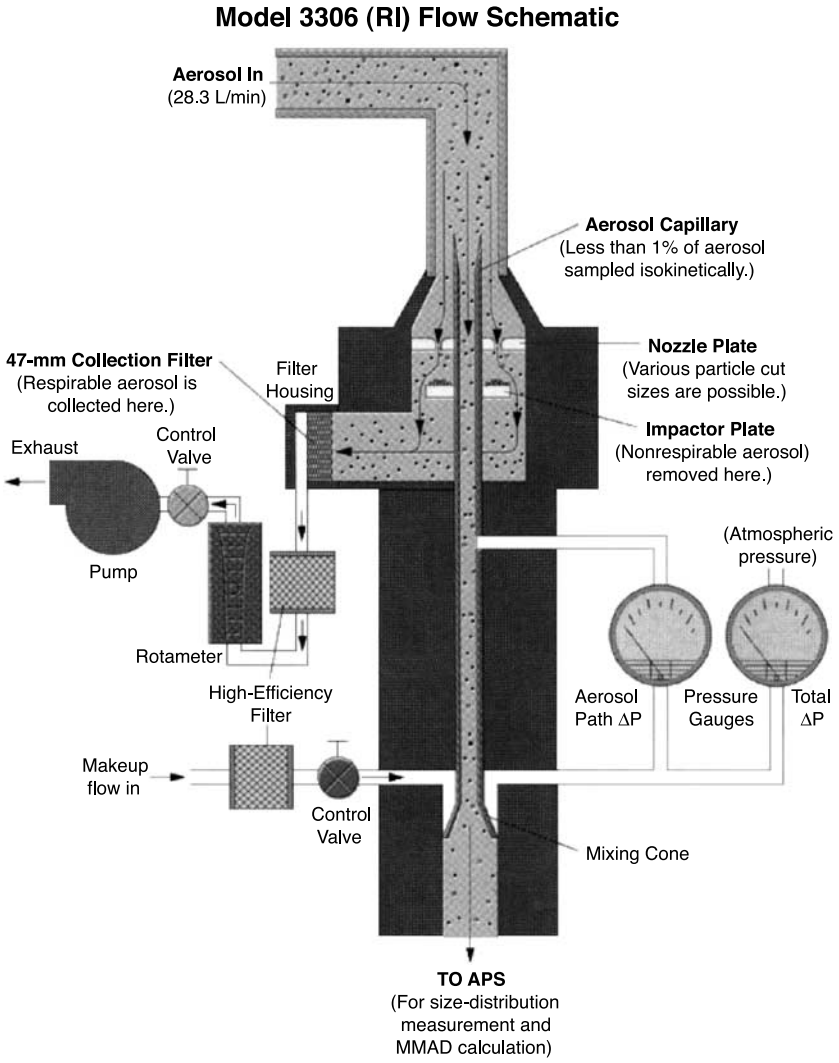


***Figure 1.*** Flow schematic of Model 3306 Impactor Inlet.

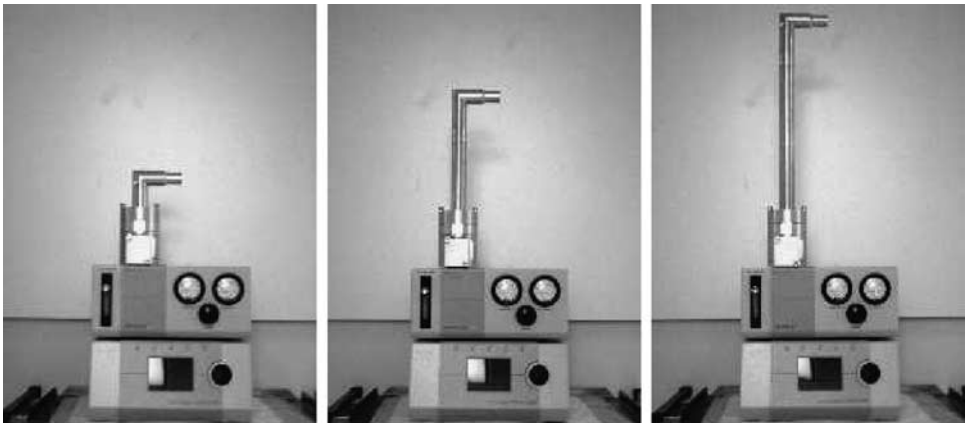

*Figure 2.* Photograph of TSI Model 3306 (top module) with 0 cm, 20 cm and 40 cm vertical extensions. The bottom module is the Model 3321 Aerodynamic Particle Sizer (APS).

3306 Impactor Inlet. The Model 3306, as supplied by the manufacturer, does not have an extension. Previous studies have suggested the need for extensions after the USP Inlet.[5,6] This study investigates this need further by evaluating solution MDIs using the 3 different configurations; as supplied by the manufacturer (denoted 0 cm), with a 20 cm extension (20 cm), and with a 40 cm extension (40 cm). Figure 2 shows the Model 3306 without an extension (0 cm) as well as with 20 cm and 40 cm vertical extensions interfaced between the Model 3306 and the USP Inlet.

## EXPERIMENTAL METHODS

### Materials

The pressure resistant glass aerosol vials, 50 mcl Spraymiser™ valves, QVAR™ actuator (orifice diameter of 0.3 mm) and beclomethasone dipropionate (BDP) used in this study were provided by 3M Drug Delivery Systems (St. Paul, MN). 1,1,1,2-Tetrafluoroethane (HFA 134a; Dymel® 134a) was obtained from DuPont Chemicals (Wilmington, DE) and ethanol (200 proof) from Aaper Alcohol and Chemical Company (Shelbyville, KN). All other solvents were obtained from Aldrich Chemical Company (Milwaukee, WI) and were used as received.

### Formulations

Nine solution MDIs containing various BDP and ethanol concentrations were prepared in pressure resistant glass vials. MDIs were formulated with varying amounts of BDP and ethanol to investigate the effects of non-volatile and semi-volatile formulation constituents (Table 1). It was not possible to investigate the high drug concentration (0.8% w/w) at the 5% and 10% w/w ethanol concentration due to solubility limits. Likewise, it was not possible to evaluate the medium drug concentration (0.4% w/w) at 5% w/w ethanol. For all the formulations prepared, BDP and ethanol (200 proof) were directly weighed into pressure resistant glass vials. Vials were sonicated until a clear solution was obtained. The ''cold fill'' technique was used to fill the vials with HFA 134a. Each of these vials were immediately crimped with 50 mcl Spraymiser™ valves (3M Drug Delivery Systems, St. Paul, MN) using a small scale bottle crimper (Model 3000B, Aerotech Laboratory Equipment Company, Maryland, NY). Vials were inspected with a laser tyndall beam in order to make sure that all the components in the vial were in solution.

*Table 1.* Formulations used for product performance study.

| | BDP concentration | Ethanol concentration | HFA-134a |
|---|---|---|---|
| Formulation | (% w/w) | (% w/w) | (% w/w) |
| 1 | 0.08 | 5 | 94.92 |
| 2 | 0.08 | 10 | 89.92 |
| 3 | 0.40 | 10 | 89.60 |
| 4 | 0.08 | 15 | 84.92 |
| 5 | 0.40 | 15 | 84.60 |
| 6 | 0.80 | 15 | 84.20 |
| 7 | 0.08 | 20 | 79.92 |
| 8 | 0.40 | 20 | 79.60 |
| 9 | 0.80 | 20 | 79.20 |

### Product Aerodynamic Particle Size Characterization

Prior to each measurement, the stages of the ACI and the components of the Model 3306 actor Inlet were thoroughly cleaned with methanol and dried in a stream of dry air. The same QVAR™ actuator was used for all the testing. For each experiment in the series, the sample vial was actuated five times in order to prime the valve and the stem of the valve was subsequently cleaned with the mobile phase (70:30-ACN: Water). The valve stem and actuator were then dried with a stream of dry air and the vial was fitted to the clean actuator. The flow rate through the ACI and Model 3306 was adjusted to 28.3 L/min using a flow meter (TSI series 4000). Triplicate analyses were done using each vial for the ACI and Model 3306 experiments (0 cm, 20 cm and 40 cm extensions). After collecting the sample, the valve stem and the actuator were quantitatively rinsed with the mobile phase for chemical analysis.

For the ACI, the valve stem, actuator, USP Inlet, stages 0–7 and the filter were rinsed with known volumes of the mobile phase and the amount of drug present on each stage was determined by HPLC assay. The coarse particle mass for the ACI tests was defined as the sum of the mass analytically determined on stages 0, 1 and 2. The fine particle mass for the ACI was defined as the sum of the mass analytically quantitated on stages 3 through the filter (this corresponds to particles with aerodynamic diameters less than about 4.7 μm – the same size used to define the fine particle mass for the Model 3306 tests).

Chemical analysis of the Model 3306 consisted of the valve stem, actuator, USP Inlet, the 20 cm or 40 cm extension, impactor plate and the filter. The MDI assembly was coupled with the Model 3306 USP Inlet using a mouthpiece adaptor to ensure a good fit between the actuator and the USP Inlet. Each vial was actuated 5 times during the data collection period of 40 seconds. Chemical analysis of the drug on the USP Inlet, extensions (20 cm or 40 cm), impactor plate and the filter were performed by dissolving the drug present on each component using known volumes of the mobile phase. The drug on the impaction plate was recovered by wiping the plate several times with cotton tipped swab that had been saturated with mobile phase. The cotton tip was then placed in a known volume of mobile phase for 5 minutes. Similarly the filter (47 mm glass fiber filter, Gelman Laboratory, Ann Arbor, MI) was rinsed thoroughly with the mobile phase. After collecting the samples, the entire assembly was thoroughly rinsed with methanol and dried in a stream of dry air. A new filter was used for each measurement. The impaction plate and the filter samples were filtered with 0.2 μm Acrodisc© filters (Pall Gelman Laboratories, Ann Arbor, MI) prior to analysis.

## HPLC ASSAY

The HPLC system consisted of a Waters 2690 separation module (Waters, Milford, MA) coupled with a Waters 996 Photodiode array (PDA) detector. Sample analysis was performed by a reverse-phase HPLC assay, using a $150 \times 4.6$ mm, 5 μm Apollo C18 column, maintained at ambient temperature. Acetonitrile:Water (70:30) was used as the mobile phase, at a flow rate of 0.8 mL/min with an injection volume of 50 μL. Ultraviolet detection was done at 240 nm and the retention time was 2.7 minutes. Quantification was done based on peak area, using a standard curve prepared daily. The HPLC system suitability tests verified that the reproducibility of the system was adequate for each analysis performed.

## RESULTS

In order to isolate and compare the drug deposition for each instrument and configuration, the results of the chemical analysis of the ACI, Model 3306 components, and inhaler components are reported as the percent of total drug recovered for each test. The total recovery of BDP for all the MDIs was within 10% of the theoretically expected total for each test based on the concentration of drug in the formulation and the valve delivery. Results of the chemical analysis for the Model 3306 are reported for 3 different configurations; as supplied by the manufacturer (0 cm extension) and using 20 cm and 40 cm extensions and are compared directly to those obtained from ACI testing. The BDP recovered on the valve stem was minimal (less than 3% of total) and can be considered insignificant for data analysis.

### Actuator

The average BDP recovered on the actuator, along with the standard deviations, is shown in Table 2. The values are reported as the percentage of total drug recovered and are averages of three replicates. Actuator recoveries remained nearly constant at $18.8\% \pm 1.4\%$ for the various solution MDIs. Not surprisingly, significant differences between actuator depositions were not observed between the ACI and Model 3306 configurations.

***Table 2.*** Percentage of total BDP recovered from the actuator.

| Formulation | | | | Actuator (% of total BDP recovered) | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| BDP (%w/w) | Ethanol (%w/w) | ACI | S.D. (n=3) | 0 cm | S.D. (n=3) | 20 cm | S.D. (n=3) | 40 cm | S.D. (n=3) |
| 0.08 | 5 | 17.83 | 0.72 | 16.57 | 1.31 | 17.96 | 1.78 | 18.68 | 0.65 |
| 0.08 | 10 | 18.36 | 1.68 | 21.21 | 1.43 | 19.50 | 1.29 | 19.22 | 1.87 |
| 0.40 | 10 | 17.89 | 1.06 | 18.32 | 0.17 | 17.55 | 2.03 | 18.64 | 1.81 |
| 0.08 | 15 | 18.91 | 0.95 | 19.59 | 0.95 | 18.90 | 0.72 | 18.79 | 1.27 |
| 0.40 | 15 | 19.50 | 1.33 | 19.46 | 1.61 | 18.34 | 0.73 | 20.06 | 1.50 |
| 0.80 | 15 | 17.59 | 1.25 | 18.30 | 0.61 | 18.72 | 1.30 | 17.83 | 0.30 |
| 0.08 | 20 | 21.11 | 0.64 | 20.04 | 1.04 | 19.54 | 0.57 | 19.07 | 0.95 |
| 0.40 | 20 | 18.99 | 0.37 | 18.77 | 0.66 | 18.68 | 0.97 | 20.11 | 0.94 |
| 0.80 | 20 | 18.26 | 1.02 | 18.85 | 0.43 | 18.21 | 0.58 | 18.35 | 0.55 |

## USP Inlet

The wide range of formulations gave USP Inlet depositions from 15% to 50%. Figure 3 shows the Inlet deposition relationship between the ACI and the three configurations of the Model 3306. The results obtained with the various Model 3306 configurations were highly correlated to the results from the ACI ($r^2 > 0.95$) and with slopes near unity ($1.0 \pm 0.05$). In general, it was observed that as the ethanol concentration in the formulation increased the USP Inlet deposition increased. For a given ethanol concentration the USP Inlet deposition was independent of the drug concentration in the formulation.

## Extensions (20 cm and 40 cm)

Drug deposition on the walls of the vertical inlet extensions was characterized to ensure there was not significant drug loss on the extensions. For the 54 different experiments conducted using the 20 cm and 40 cm extensions, only 4 experiments had quantifiable BDP amounts recovered from the extensions. In all cases the drug deposition on the additional extension length was less than 1.1% of the total drug delivered and can therefore be concluded to not cause significant aerosol loss.

## Coarse Particle Deposition

The BDP collected on the single-stage impaction plate is defined as the coarse particle mass. For comparison with the ACI, the combined recoveries on the stages 0 through 2, is taken to be equivalent to the recovery on the single stage impaction plate. Figure 4 shows the percent of total BDP recovered on the impaction plate for the three configurations of the Model 3306 (0 cm, 20 cm and 40 cm) and the combined

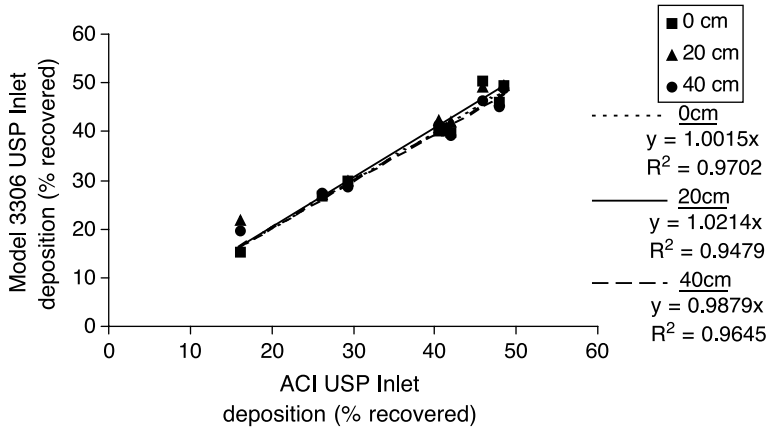


***Figure 3.*** Relationship between the drug recovered on the USP inlet for three impactor inlet configurations (0 cm, 20 cm and 40 cm) and Andersen Cascade Impactor (ACI).

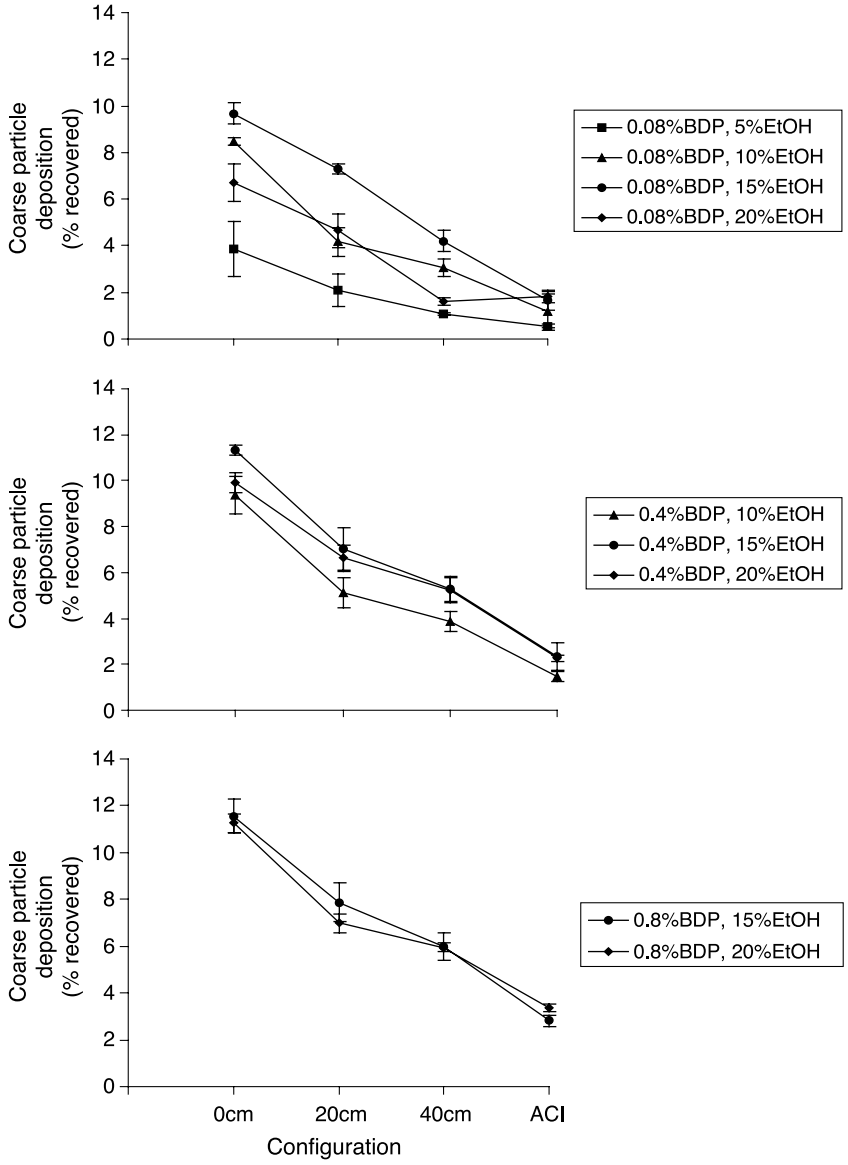


***Figure 4.*** Comparison of coarse particle deposition for the Model 3306 Impactor Inlet (single-stage with 4.7 μm cutpoint) using three configurations (0 cm, 20 cm and 40 cm) and ACI (stages 0 through 2).

recoveries of the ACI. From Fig. 4 it is evident that the coarse particle deposition is systematically lower for the ACI than for the various Model 3306 configurations. The greatest divergence is for the Model 3306 configuration that does not have a vertical extension. The average difference in the coarse particle mass for the Model 3306 without the extension (0 cm) and the ACI is about 8%. As the extension length is increased, the coarse particle mass obtained from the Model 3306 approaches that obtained from the ACI testing. The average difference between the plate recoveries for the ACI and the Model 3306 with the 20 cm extension and 40 cm extensions are 4% and 2%, respectively. The smallest deviation between the two systems occurred for the formulation containing 5% w/w ethanol. For the formulations evaluated, as the ethanol concentration in the formulation increased the coarse particle deposition increased and showed greater deviation between the Model 3306 and the ACI. For a given ethanol concentration the coarse particle deposition was independent of the drug concentration in the formulation.

### Fine Particle Deposition

In this analysis, the aerosol passing through the 4.7 μm cutpoint impactor stage and collecting on the filter of the Model 3306 is defined as the fine particle deposition. For the ACI, total drug recovered on the stages 3 through 7 and the filter, is considered to be the fine particle deposition. Figure 5 shows the fine particle deposition for the ACI and the three Model 3306 configurations. For the formulations tested, average filter deposition for the Model 3306 ranged from 20% to 60%. There was no statistical difference between the fine particle mass for the three Model 3306 configurations and the ACI for the 5% ethanol formulation. For the intermediate and high ethanol concentrations the fine particle deposition for the 0 cm configuration

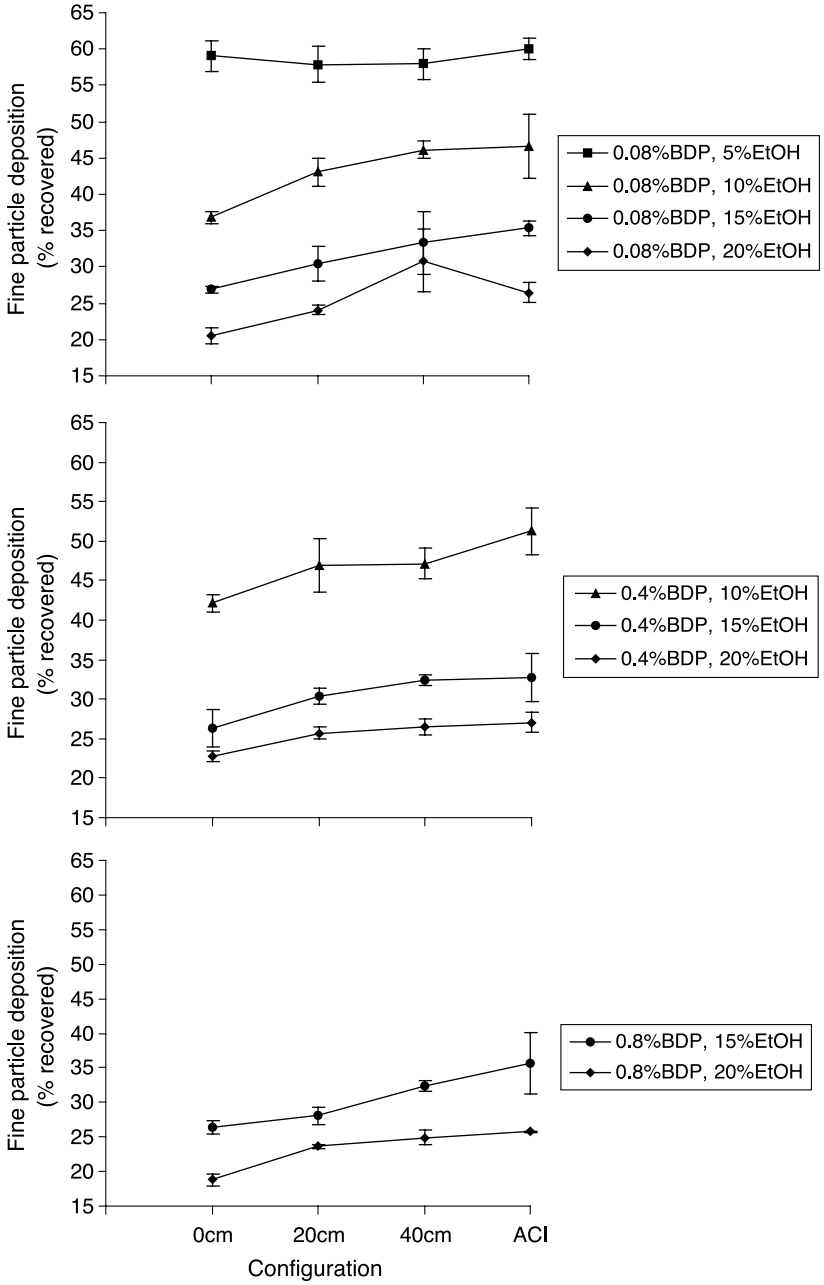


***Figure 5.*** Comparison of fine particle deposition for the Model 3306 Impactor Inlet (single-stage with 4.7 μm cutpoint) using three configurations (0 cm, 20 cm and 40 cm) and ACI (stages 3 through 7 and filter).

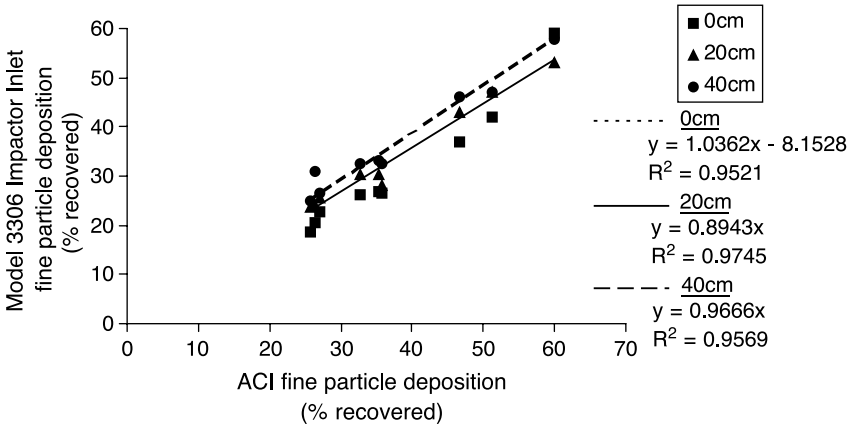


***Figure 6.*** Fine particle mass correlations between the ACI and Impactor Inlet with 0 cm, 20 cm and 40 cm extensions.

is systematically lower than for the ACI values. As the vertical extension length is increased the values converge to those obtained from the ACI testing.

Figure 6 shows the relationship between the fine particle deposition for the ACI and the three configurations of the Model 3306. In general, the fine particle deposition between the ACI and the Model 3306 correlated well and had near unity slopes. However, while the data collected without an extension (0 cm) has a slope near unity, there is also a significant negative intercept. This indicates that the ACI gave a higher fine particle deposition than the Model 3306. For the 20 cm and 40 cm configurations, there is not a statistically significant intercept and the correlations are still near unity. For the formulations evaluated, as the ethanol concentration in the formulation increased the fine particle deposition decreased and showed greater deviation between the Model 3306 and the ACI. These results are consistent with the coarse particle deposition, which increased with an increase in the ethanol concentration. For a given ethanol concentration the fine particle deposition was independent of the drug concentration in the formulation.

## DISCUSSION

The goal of the study was to evaluate the TSI Model 3306 Impactor Inlet as a testing instrument for MDIs and to compare results obtained with this instrument to the more labor intensive Andersen Cascade Impactor (ACI). Not surprisingly, nearly identical results were obtained for the valve stem, actuator and USP Inlet since these components were identical for both instruments. The motivating aspect of this investigation was the comparison of the 'coarse particle' and 'fine particle' depositions.

This study suggests that in order to obtain results that are comparable between the two instruments, a vertical extension between the USP Inlet and Model 3306 may be necessary. Whether an extension is needed and the length of the extension needed appears to be formulation dependent. In this study it is clear that as the concentration of ethanol in the formulation increased above 5% w/w, the 20 cm and 40 cm vertical extensions gave improved correlations between the two instruments. The Model 3306 plate deposition (coarse deposition), when compared to the total recoveries on the ACI stages 0 through 2, was observed to be significantly higher for the Model 3306 configuration without an extension (0 cm). The incorporation of the 20 cm and 40 cm extensions systematically decreased the plate deposition, giving results closer to the ACI results.

The extension lengths do not appear to adversely affect the aerosol flow. A possible explanation for the low wall deposition is that the extensions merely serve as an additional length to the vertical portion of the USP Inlet. It has been suggested that the USP Inlet deposition results from turbulence induced by the large difference in velocities of the bulk airflow in the USP Inlet and the MDI plume and occurs predominantly in the first 2 or 3 cm of the Inlet.[7] This turbulence subsides after the aerosol exits the vertical segment of USP Inlet, and as a result, minimal aerosol deposition is observed on the additional extensions.

The cause of the differences in 'coarse particle' and 'fine particle' deposition obtained between the ACI and Model 3306 are not yet fully understood. The cutpoint of the Model 3306 and the cutpoint of Stage 2 of the ACI are both reported by the manufacturers to

be 4.7 μm.[8,9] Differences in the true cutpoints of these impactor stages could cause systematic differences in the 'coarse particle' and 'fine particle' deposition for these two instruments. The cutpoint of stage 2 of the ACI has been reported to be 5.7 μm[10] and 5.0 μm[11] and has been shown to vary from impactor to impactor.[12] While this could account for a systematic difference between the 2 instruments, this does not appear to be the primary cause of the difference since the magnitude of the difference changes when vertical Inlet extensions are used.

It is more likely that the observed differences in the 'coarse particle' and 'fine particle' deposition are related to the evaporation of the atomized aerosol generated during each actuation. MDI aerosols are very dynamic and change drastically during the aerodynamic size measurements described in this paper. The atomized droplets contained propellant, ethanol, and BDP. It is often assumed that the propellant and ethanol have fully evaporated away before the residual drug particles are measured. However, ethanol containing droplets were observed to collect on the top two stages of the ACI and on the Model 3306 impaction plate when ethanol sensitive paper was adhered to these impaction plates. Thus, the assumption that the particles are fully dry is not always valid.

The net effect of adding an extension to the Model 3306 is that aerosol droplets are allowed a longer time for evaporation. The need for an increased drying time becomes apparent when considering the physical differences between the aerosol paths of the two systems. In the Model 3306, once droplets pass through the USP Inlet they directly encounter the 'fine particle' impactor stage (4.7 μm cutpoint), whereas droplets must travel around two impactor stages prior to reaching the 4.7 μm stage in the ACI. Thus there is more time for droplets to dry in the ACI. If additional time for evaporation is not needed, then this physical difference should not be of practical significance.

The fine particle deposition values for the three Model 3306 configurations and ACI were found to correlate the best for the 5% ethanol formulations. This suggests that for formulations having little or no semivolatile components, the Model 3306 may yield acceptable results without an extension. However, significant deviations between the fine particle deposition values were observed between 0 cm extension and the ACI for the formulations having ethanol concentrations between 10% and 20% w/w. The fine particle deposition values for different extension lengths converge to the ACI values, as the extension length is increased. This is a direct result of decreased deposition on the impaction plate due to increased droplet evaporation as discussed above, which manifests as an increase in fine particle mass. From the present study it is evident that a vertical extension may be required in order to achieve comparable results from the Model 3306 and the ACI due to the dynamic MDI aerosols. This is especially applicable to high cosolvent formulations. The testing in this work used the arbitrary vertical extensions of 20 cm and 40 cm, thus others could be considered. However, even with subtle differences in absolute values, it is important to understand that aerosols are dynamic and are often changing as measurements are being made. The ACI characterizes the aerosol at one point in the dynamic process, the Model 3306 at a slightly different point. To conclude one is more appropriate than the other is debatable. Nonetheless, both instruments provide insight into the expected respirability of MDI aerosols. Either instrument can be used to characterize MDI aerosols, but it is important to recognize there may be slight differences depending on which instrument is used.

## CONCLUSION

It has been shown that in order to obtain comparable results between the TSI Model 3306 Impactor Inlet and the Andersen Cascade Impactor (ACI), an extension to the USP Inlet may be necessary. The choice of the extension length is dependent on the formulation, which in this study appears to be dependent on the ethanol concentration. These preliminary studies suggest that the Model 3306 Impactor Inlet may become a valuable tool in the rapid screening of solution MDIs.

## REFERENCES

1. United States Pharmacopeia. *USP26/NF21. <'601> Aerosols*; United States Pharmacopeial Convention: Rockville, MD, 2003.
2. Hallworth, G.W.; Westmoreland, D.G. The twin impinger: a simple devise for assessing the delivery of drugs from metered dose pressurized aerosol inhalers. J. Pharm. Pharmacol. **1987**, *39*, 966–972.
3. Stein, S.W.; Gabrio, B.J.; Oberreit, D.; Hairston, P.; Myrdal, P.B.; Beck, T.J. An evaluation of mass-weighted size distribution measurements with the Model 3320 aerodynamic particle sizer. Aerosol Sci. Technol. **2002**, *36*, 1–10.
4. Stein, S.W.; Myrdal, P.B.; Gabrio, B.J.; Obereit, D.; Beck, T.J. Evaluation of a new aerodynamic

particle sizer spectrometer for size distribution measurement of solution metered dose inhalers. J. Aerosol Med. **2003**, *16* (2), 107–119.
5. Stein, S.W.; Beck, T.J.; Gabrio, B.J. In *Evaluation of a New Aerodynamic Particle Sizer Spectrometer for MDI Size Distribution Measurements*, Proceedings of Respiratory Drug Delivery VII, Tarpon Springs, Florida, May 14–18, 2000; Byron, P.R., Dalby, R.N., Farr, S.J., Peart, J., Eds.; Serentec Press: Raleigh, NC, 2000; 283–286.
6. Gupta, A.; Myrdal, P.B.; Stein, S.W.; Gabrio, B.J.; Beck, T.J. In *Comparison of the TSI Model 3306 Impactor Inlet with the Andersen Cascade Impactor by Testing Solution Metered Dose Inhalers*, Proceedings of Respiratory Drug Delivery VIII, Tucson, AZ, May 12–16, 2002; Byron, P.R., Dalby, R.N., Farr, S.J., Peart, J., Eds.; Serentec Press: Raleigh, NC, 2002; 659–662.
7. Stein, S.W.; Gabrio, B.J. In *Understanding Throat Deposition During Cascade Impaction Testing*, Proceedings of Respiratory Drug Delivery VII, Tarpon Springs, Florida, May 14–18, 2000; Byron, P.R., Dalby, R.N., Farr, S.J., Peart, J., Eds.; Serentec Press: Raleigh, NC, 2000; 287–290.
8. Graseby-Andersen, Inc. *I ACFM Non-Viable Ambient Particle Sizing Sampler Operating Manual*; Graseby-Andersen, Inc.: Smyrna, GA, 1985.
9. TSI Incorporated Particle Instruments. *Model 3306 Impactor Inlet Operating Manual*; TSI Incorporated Particle Instruments: St. Paul, MN, 2003.
10. Vaughan, N.P. The Andersen Impactor: calibration, wall losses and numerical simulation. J. Aerosol Sci. **1989**, *20* (1), 67–90.
11. Mitchell, J.P.; Costa, P.A.; Waters, S. An assessment of Andersen Mark-II cascade impactor. J. Aerosol Sci. **1988**, *19* (2), 213–221.
12. Stein, S.W. Size distribution measurements of metered dose inhalers using Andersen Mark II cascade impactors. Int. J. Pharm. **1999**, *186*, 43–52.