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# Reducing bounce effects in the Andersen cascade impactor

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**Abstract**

The collection efficiency of the Andersen cascade impactor (ACI) can be affected by particle bounce, overload and re-entrainment (or blow-off), collectively referred to as bounce effects. Reduction of bounce effects in the ACI operated at 60 LPM was investigated for placebo large porous particles. Aerodynamic particle size distributions (aPSDs) obtained with the ACI and multi-stage liquid impinger (MSLI) were compared by observation of modes and statistical comparisons of the mass median aerodynamic diameter (MMAD) and geometric standard deviation ($\sigma_g$). Particle bounce effects were prevalent in the ACI with uncoated plates, i.e., bi-modal distribution with statistically significant differences in MMAD and $\sigma_g$ ($P < 0.05$). Coating the impaction plates with a thin layer of vacuum grease and decreasing the ACI stage jet velocities reduced, but did not minimize bounce effects. Bounce effects were minimized using 20-μm pore glass fiber filters saturated in water placed on inverted impaction plates, with good agreement obtained between the ACI and MSLI aPSDs, i.e., mono-modal with no statistically significant differences in MMAD and $\sigma_g$ ($P > 0.05$). Selection of the impaction substrate material and solvent must be evaluated with the drug product and analytical methods to minimize bounce effects and obtain an accurate measure of the aPSD.


*Keywords:* Bounce effects; Cascade impaction; Large porous particles

## 1. Introduction

The eight-stage Andersen cascade impactor (ACI) is widely used to characterize and control the aerodynamic particle size distribution (aPSD) emitted from therapeutic inhalation aerosols (Mitchell and Nagel, 2004). The method is described in the United States and European Pharmacopoeias and has been the Food and Drug Administration's method of choice for the release and stability testing of pharmaceutical inhalation products (EP, 1997, USP<601>). Particle engineering has emerged as a potential new technique to enhance the performance of therapeutic inhalation aerosols (Edwards et al., 1997; Duddu et al., 2002). However, modification of the particle density, morphology and material may affect the impactor's collection efficiency. This is especially the case for particles with large volumes, low envelope densities and small contact surface areas, e.g., large porous particles (Edwards et al., 1997). Also, recovery of the active ingredient

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is prerequisite for therapeutic aerosols in order to satisfy the mass balance of the product label claim (FDA, 1998; USP<601>). Therefore, selection of impaction coating films and substrates must be integrated with the drug, excipients and chemical analysis.

The collection efficiency of an impactor stage is defined as the cumulative fraction of particles that pass downstream of the stage relative to the particles collected upstream, and is usually expressed as a function of Stokes number or aerodynamic diameter (Marple and Rubow, 1986). Factors affecting the accuracy and robustness of the collection efficiency include particle bounce, overload, re-entrainment (or blow-off) and interstage losses. Bounce occurs when the impulse of an impacting particle is greater than the adhesion force. This results in the particles being carried to downstream stages where the jet velocities are higher, increasing the incidence of bounce and distorting the aPSD toward smaller sizes. Overload occurs when large volumes of particles are deposited, modifying the collection efficiency of the impaction surface. Re-entrainment refers to particles that have impacted on a surface and are subsequently removed either by the force of the impinging jet, cross-flow from adjacent jets or other impacting particles. Particle bounce, stage overload and re-entrainment are interactive effects and are difficult to identify individually. Therefore, they are generally referred to as bounce effects. Interstage losses are defined as the percentage of particles collected on the impactor stages (rather than the impaction plates) relative to the total mass collected in the impactor (USP<601>).

The purpose of this study was to evaluate bounce effects in the ACI with placebo large porous particles. Coating the impaction plates with a compliant film, reducing the stage jet velocities, and the introduction of porous substrates were evaluated. Comparisons were made with aPSDs obtained with the multi-stage liquid impinger (MSLI). The MSLI utilizes liquid impaction surfaces which prevent bounce effects that occur with solid impaction surfaces (Asking and Olsson, 1997).

## 2. Materials and methods

The eight-stage Andersen cascade impactor (Thermo Electron, Franklin, MA) and multi-stage liquid impinger (Erweka USA Inc., Milford, CT) were used to obtain the aPSD emitted from the AIR® delivery system (Dunbar et al., 2002). Both impactors included a USP induction port and were operated at 60 LPM for a total air volume of 2 L (FDA, 1998; USP<601>). HPLC grade methanol was used as the stage solvent in the MSLI. The placebo large porous particles contained 0.1% (w/w) rhodamine B. Sample solutions were prepared by dilution with methanol (HPLC grade) into 50-mL volumetric flasks. Chemical analysis was performed using fluorescence spectrophotometry ($\lambda_{ex}$ = 547 nm; $\lambda_{em}$ = 567 nm) (F-4500, Hitachi Inst., San Jose, CA). The studies were conducted with 5- and 10-mg powder fill weights. The ACI was evaluated using uncoated and coated impaction plates (thin layer of vacuum grease applied by hand—Dow Corning, Midland, MI) with impactor stages 0 to 7 (0:7) and stages −1 to 6 (−1:6) (Thermo Electron, Franklin, MA). Glass fiber filters (Cat #28313-057, VWR Brand, West Chester, PA) were evaluated as both dry and wet (HPLC grade water) substrates placed on inverted impaction plates.

The weighting effect introduced by the non-uniform stage widths of the ACI and MSLI were normalized by calculating the mass frequency ($p\,(d_i)$) as a continuous function of the aerodynamic diameter ($d_i$), as follows (Dunbar and Mitchell, 2005):

$$p(d_i) = \frac{m_i}{M_e}\frac{1}{\Delta d_i} \tag{1}$$

where:

$$d_i = \frac{\mathrm{ECD}_{i-1} + \mathrm{ECD}_i}{2} \tag{2}$$

and $\mathrm{ECD}_i$ is the effective cut-off diameter of stage $i$, $m_i$ is the mass recovered from stage $i$, $M_e$ is the mass emitted from the delivery system and $\Delta d_i$ is the width of the particle size interval:

$$\Delta d_i = \mathrm{ECD}_{i-1} - \mathrm{ECD}_i \tag{3}$$

The ECDs for the MSLI and ACI operated at 60 LPM are summarized in Table 1.

Comparisons of the mass frequencies obtained by ACI and MSLI were performed by observing modes, and conducting a comparison of means for the mass median aerodynamic diameter (MMAD) and geomet-

Table 1
Calibrated effective cut-off diameters at 60 LPM

| Cascade impactor | −1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|
| MSLI[a] (μm) | – | – | 13.4 | 6.8 | 3.1 | 1.7 | – | – | – |
| ACI 0:7[b] (μm) | – | 5.6 | 4.3 | 3.4 | 2.0 | 1.1 | 0.5 | 0.3 | 0.1 |
| ACI −1:6[c] (μm) | 8.6 | 6.5 | 4.4 | 3.3 | 2.0 | 1.1 | 0.5 | 0.3 | – |

[a] Asking and Olsson (1997).
[b] Nichols and Smurthwaite (1998).
[c] Thermo Electron, Franklin, MA.

ric standard deviation ($\sigma_g$), given by:

$$\sigma_g = \frac{\text{MMAD}}{d_{0.16}} \quad (4)$$

where $d_{0.16}$ is the diameter at the 16th percentile of the cumulative distribution undersize. MMAD and $d_{0.16}$ were obtained by interpolation from the cumulative mass fraction undersize:

$$\text{Cumulative mass fraction} < \text{ECD}_i = \frac{1}{M_e} \sum_{j=\text{Filter}}^{\text{Stage } i+1} m_j \quad (5)$$

The non-linear least-squares fit of the log-normal probability density function was superimposed on the experimental data to assist with the visualization of the continuous aPSD (Dunbar and Hickey, 2000). However, this does not assume the log-normal probability density function accurately represented the aPSDs (Dunbar and Hickey, 2000). Statistical analysis of experimental designs was performed using a factorial ANOVA model (Design Expert v5, Stat-Ease Inc., Minneapolis, MN). Statistical comparison of means was conducted using Dunnett's method with the MSLI as the control at an $\alpha$-level = 0.05 (JMP, SAS Institute, Cary, NC).

## 3. Results

Fig. 1(a) and (b) compare the MSLI and ACI aPSDs, obtained with stages 0:7 using uncoated and coated impaction plates, respectively. Bounce effects were prominent with uncoated impaction plates, reflected by the bi-modal distribution, with the maximum mode occurring at 0.05 μm (representing the mass collected on the filter stage). Coating the impaction plates with a thin layer of vacuum grease reduced the mode at 0.05 μm; however, the aPSD remained bi-modal. The mass balance from coated impaction plates, summarized in Table 2, was reduced by approximately 10% of the powder fill weight, relative to uncoated impaction plates and the MSLI.

The ACI aPSDs obtained with stages −1:6 using uncoated and coated impaction plates were also bi-

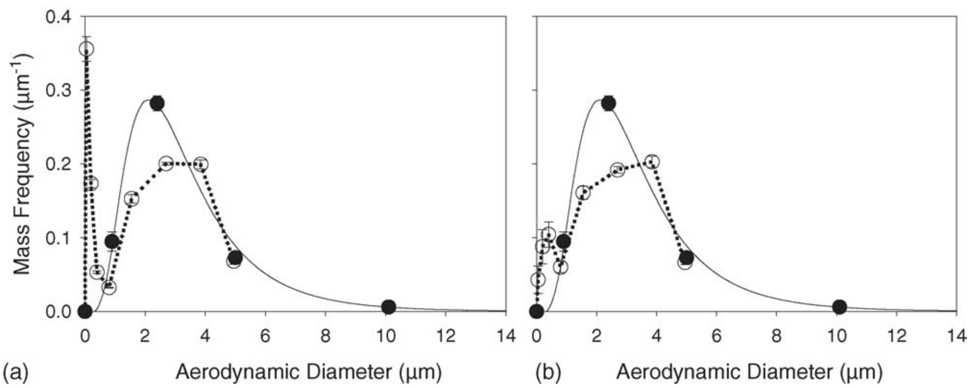


Fig. 1. aPSD obtained by MSLI (closed circle) and ACI (open circle) configured with stages 0:7 using (a) uncoated plates, and (b) coated plates (standard deviations shown; $n = 3$).

Table 2
Mass balance summary (standard deviations shown in parenthesis; $n = 3$)

| Cascade impactor | Impaction surface | Mass balance (%)[a] |
|---|---|---|
| MSLI | Glass frit plus methanol | 100 (2) |
| ACI 0:7 | Uncoated plate | 104 (2) |
| | Coated plate | 90 (3) |
| ACI −1:6 | Uncoated plate | 105 (0) |
| | Coated plate | 95 (2) |
| | 20-μm glass fiber filter + water | 98 (5) |

[a] Relative to powder fill weight.

Table 3
Parameters and levels for $2^3$ full factorial design

| Factor | Name | Units | (−) | (+) |
|---|---|---|---|---|
| A | Pore size | μm | 2 | 20 |
| B | Water | – | No | Yes |
| C | Fill weight | mg | 5 | 10 |

modal, as illustrated in Fig. 2(a) and (b), respectively. Bounce effects were less prominent with uncoated plates using stages −1:6 relative to stages 0:7. The mode at 2.65 μm obtained by the ACI suggested that stage 3 may have become overloaded, with particles impacting on this stage bouncing to downstream stages. The mass balance from coated impaction plates using the −1:6 stage configuration increased by 5% of the powder fill weight relative to the 0:7 stage configuration (Table 2).

A $2^3$ full factorial design, summarized in Table 3, was performed to evaluate the use of glass fiber filters as an impaction plate substrate. The response factor was the mass depositing on the filter stage as a percentage of the initial fill weight. The mass deposited on the filter stage was indicative of bounce effects in the earlier uncoated/coated impaction plate studies, and should tend to zero as bounce effects are minimized. A statistically significant second order interaction was observed between filter pore size and solvent, as illustrated in Fig. 3(a) ($P < 0.05$). Increasing the pore size from 2 to 20 μm and saturating the filter with water significantly reduced the mass of powder depositing on the filter stage, as illustrated in Fig. 3(b) ($P < 0.05$). Also, increasing the powder fill weight from 5 to 10 mg did not have a statistically significant effect on the filter mass deposit ($P > 0.05$). The aPSD obtained with the ACI (stages −1:6) using saturated 20-μm glass fiber filters was mono-modal, indicating that bounce effects had been minimized, and showed good agreement with the MSLI (Fig. 4).

Table 4 summarizes the aPSDs in terms of the modes, MMAD and $\sigma_g$ obtained by the MSLI and the various ACI configurations. The ACI (stages −1:6) using saturated 20-μm glass fiber filters produced a single mode aPSD with no statistically significant differences in MMAD and $\sigma_g$ relative to the MSLI ($P > 0.05$). Differences were observed between the ACI configurations using uncoated and coated impaction plates relative to the MSLI, producing bi-modal aPSDs and statistically significant differences in MMAD and $\sigma_g$ ($P < 0.05$).

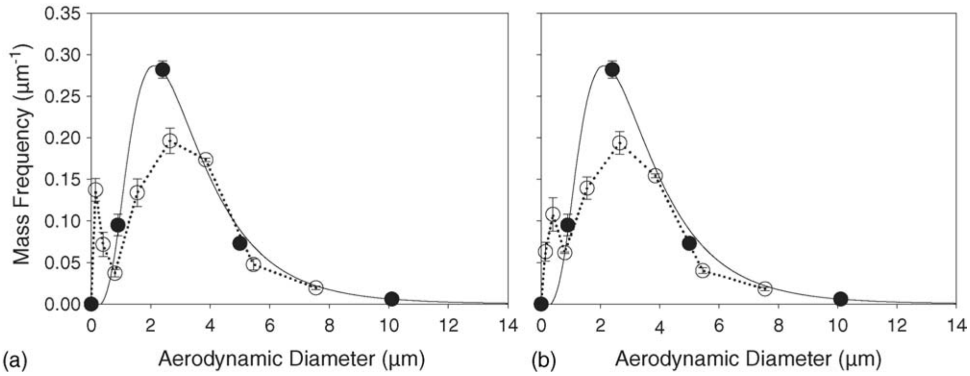


Fig. 2. aPSDs obtained by MSLI (closed circle) and ACI (open circle) configured with stages −1:6 using (a) uncoated plates, and (b) coated plates (standard deviations shown; $n = 3$).

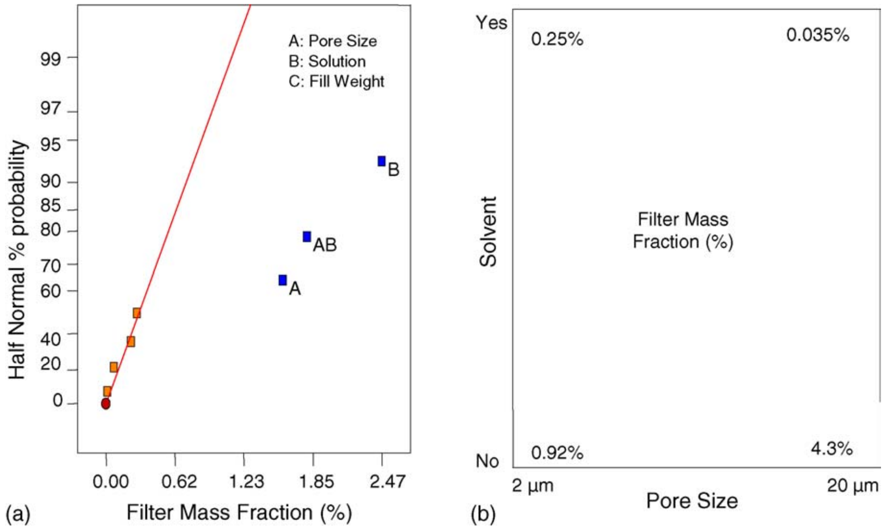


Fig. 3. Filter mass fraction (a) half-normal plot of effects; (b) solvent-pore-size interaction.

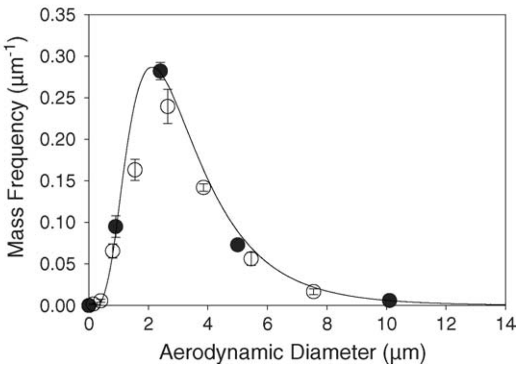


Fig. 4. aPSDs obtained by MSLI (closed circle) and ACI (open circle) configured with stages −1:6 using 20-µm filter substrates saturated in water (standard deviations shown; $n = 3$).

## 4. Discussion

Bounce effects were minimized with the ACI (stages −1:6) using 20-µm glass fiber filters saturated in water, with good agreement obtained between the ACI and MSLI aPSDs. The combined action of liquid surface tension (capillary forces) and particle dissolution prevented particle-to-particle bounce (Turner and Hering, 1987). Alternative approaches to utilizing capillary forces by increasing the ambient relative humidity above 75% had yielded high collection efficiencies (>90%) for uncoated plates (Winkler, 1974; Lawson, 1980). However, elevating the ambient moisture content above normal patient use is not appropriate for assessing the routine performance of pulmonary drug products. Previous investigations of particle bounce

Table 4
Summary of representative parameters (standard deviations shown in parenthesis; $n = 3$)

| Cascade impactor | Configuration | Mode (µm) | MMAD (µm) | GSD |
|---|---|---|---|---|
| MSLI | Glass frit + methanol | 2.4 | 3.0 (0.1) | 1.7 (0.1) |
| ACI 0:7 | Uncoated | 0.05, 2.7 | 3.3 (0.0) | 2.2[a] (0.0) |
| | Coated | 0.4, 3.85 | 3.4[a] (0.1) | 2.1[a] (0.1) |
| ACI −1:6 | Uncoated | 0.15, 2.65 | 3.6[a] (0.2) | 2.1[a] (0.1) |
| | Coated | 0.4, 2.65 | 3.6[a] (0.2) | 2.1[a] (0.0) |
| | 20-µm filter + water | 2.65 | 3.2 (0.1) | 1.8 (0.0) |

[a] Statistically significantly different means relative to MSLI ($P < 0.05$).

effects have indicated that there is a strong interaction between the particle and substrate material (Esmen and Lee, 1980; Hinds et al., 1985, Turner and Hering, 1987). Saturated glass fiber filters may not be suitable for the analysis of some active pharmaceutical ingredients, for example, due to charge interactions between the particle and substrate. Therefore, selection of the impaction substrate material and solvent must be evaluated with the drug product and analytical methods to obtain an accurate measure of the aPSD.

Alternative substrates to glass fiber filters have been evaluated. A unique approach has been the use of an impaction surface with an inverse conical cavity to minimize adverse loading effects, producing collection efficiencies ≥90% for both uncoated and coated surfaces (Tsai and Cheng, 1995). Polyurethane foam (PUF) substrates have been used to absorb the kinetic energy of the impacting particles (Kavouras and Koutrakis, 2001). This approach has the advantage of eliminating coating components that may interfere with chemical analysis. High collection efficiencies were obtained with the polyurethane foam substrate (>90%). However, the PUF collection efficiency curve deviated significantly from theory, suggesting that the porous surface affected the impaction flow field.

Substrate thickness should be defined to ensure the ratio of jet diameter ($W$) to impaction plate distance ($S$) does not affect the effective cut-off diameter (ECD) after the impaction plate has been inverted. Stage ECDs are independent of the impaction plate distance when $S/W > 1$ (Marple and Rubow, 1986). Table 5 summarizes the $S/W$ ratio for stages −1 to 7 for upright and inverted impaction plates (assuming a saturated glass fiber filter thickness of 0.5 mm). ECDs for stages −1, 0 and 1 would have been different between the upright and inverted impaction plates. However, the good agreement obtained between the ACI (stages −1:6) using 20-μm glass fiber filters saturated in water and MSLI aPSDs suggests the change in impaction plate distance did not produce a significant difference in ECDs. This issue can be easily mitigated by constructing substrates that conserve the impaction plate distance.

Bounce effects were prominent with uncoated impaction plates. The problem of low collection efficiencies due to poor adhesion of solid particles on solid surfaces was recognized during the early development of the cascade impactor (May, 1945). Subsequent studies have confirmed that dry impaction surfaces yield poor collection efficiencies and distort the aPSDs due to particle bounce (Dzubay et al., 1976; Roa and Whitby, 1978a,b; Cheng and Yeh, 1979; Cushing et al., 1979; Barr et al., 1982; Markowski, 1984; Mitchell et al., 1988; Vaughan, 1989; Swanson et al., 1996). Bounce effects were still observed after coating the impaction plates with a thin layer of vacuum grease due to particles forming a monolayer for subsequent particle–particle interactions (Turner and Hering, 1987). The thickness of vacuum grease may not have been optimal for reducing particle bounce effects. It has been proposed that the ideal coating layer should be approximately equal to the radius of the particles collected (Zimon, 1982). Coating stainless steel impaction plates with a 3.75-μm film of high viscosity silicone oil minimized bounce effects for the Serevent Diskhaler® (Podczeck, 1997). However, the thickness of the coating layer becomes immaterial once a stage is overloaded (greater than a monolayer of particles) (Turner and Hering, 1987). This is of particular relevance to large porous particles that will overload a stage by volume, e.g., porous particles with a particle density of approximately 0.1 g/cc will deposit approximately 10 times the volume of particles relative to unit density particles.

Coating the impaction plates with vacuum grease hindered particle dissolution during sample recovery, reducing the mass balance, as summarized in Table 2. This is of particular importance during the quality control of drug products to satisfy the mass balance of the product label claim (FDA, 1998, USP<601>). It was

Table 5
Ratio of jet diameter ($W$) to impaction plate distance ($S$) for upright and inverted impaction plates (assuming saturated glass fiber filter thickness of 0.5 mm)

| Impaction plate configuration | −1 | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|---|---|---|
| Upright | 0.2 | 0.4 | 0.5 | 2.4 | 3.1 | 4.1 | 6.3 | 8.5 | 8.5 |
| Inverted (0.5 mm substrate) | 0.1 | 0.2 | 0.3 | 1.8 | 2.3 | 3.1 | 4.9 | 6.6 | 6.6 |

therefore concluded that coating impaction plates does not minimize bounce effects, but also hinders recovery leading to the reduction of mass balance, for particles with large volumes, low envelope densities and small contact surface areas. Interstage losses obtained with the ACI (stages −1:6) using saturated 20-μm glass fiber filters and uncoated plates (stages 0:7) were equal at 8% of the mass collected in the ACI. Interstage losses were considered to be intrinsic to the cascade impactor and independent of bounce effects.

Bounce effects were reduced by using stages −1:6 relative to stages 0:7. This was due to the lower jet velocity on stage −1 of the −1:6 stage configuration (65 cm/s) relative to stage 0 of the 0:7 stage configuration (204 cm/s). The mass balance from coated impaction plates using the −1:6 stage configuration increased by 5% of the powder fill weight relative to the 0:7 stage configuration (Table 2). This was attributed to the lower jet velocities on stage −1 reducing the particle contact with the coating layer and enhancing dissolution during recovery.

## 5. Conclusions

Bounce effects were minimized using 20-μm pore glass fiber filters saturated in water, with good agreement obtained between the ACI and MSLI aPSDs. Particle bounce effects were found to be prevalent with uncoated plates. Coating the impaction plates with a thin layer of vacuum grease and decreasing the jet velocities reduced but did not minimize bounce effects.

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