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Size distribution measurements of metered dose inhalers using Andersen Mark II cascade impactors

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Abstract

The performance of Andersen Mark II impactors was investigated theoretically and experimentally. Theoretical calculations were made to assess the impact that differences in jet diameters among Mark II impactors have on size distribution measurements of metered dose inhalers (MDIs). A previous investigation indicated that the jet diameter for stages on Mark II impactors often do not conform to the manufacturer's specifications (Stein and Olson, 1997). For the calculations reported in this paper, only jet diameters that conform to the manufacturer's specifications were considered. The calculations indicate that large differences in the amount of drug collecting on a given stage should be expected among Mark II impactors sampling an identical aerosol—even for Mark II impactors that conform to the manufacturer's specifications. These calculations suggest that it is impractical to analyze size distribution data generated with cascade impactors, such as the Mark II, on a stage-by-stage basis. Experimental measurements of three MDI products were made using three different Andersen Mark II cascade impactors. Measurements of the same product were very consistent for a given impactor, but large differences were observed in measurements of the same product with different impactors. For measurements of QVAR™ HFA beclomethasone dipropionate MDIs using three Mark II impactors, the amount of drug that collected on Stage 6 ranged from 28.7 to 41.3% of the sampled mass depending on which impactor was used. The theoretical calculations and experimental measurements reported in this paper demonstrate that it is important to consider the limited precision of cascade impactors, such as the Andersen Mark II, when analyzing the size distribution measurements that they provide.

Keywords: Andersen cascade impactor; MDI; Size distribution; Specifications; Variability

1. Introduction

Cascade impactors are widely used for measuring the size distribution of airborne particles. The Andersen Cascade Impactor (1 AFCM Non-Viable Ambient Particle Sizing Sampler, Graseby-Andersen, Smyrna, GA) is one of the most frequently used impactors for measuring the size distributions of pharmaceutical aerosols. The eight-stage Andersen impactor separates the sample aerosol into nine size intervals when used with a backup filter after the last impaction stage.

Several versions of the Andersen Cascade Impactor have been used throughout the years. The

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most commonly used versions in the pharmaceutical industry are the Mark I and Mark II impactors. The Mark I impactor was released in 1970 and has stages with cutpoints ranging from 0.4 to 11.0 μm. The Mark II impactor was released in 1977 and has cutpoints from 0.4 to 9.0 μm. The manufacturer reports that the two impactors have identical cutpoints except for the two upper stages on the Mark II which were redesigned to minimize wall losses and particle bounce (Graseby-Andersen, 1985).

In order to collect accurate data with any cascade impactor, it is necessary to have accurate data on the cutpoints of the stages. A recent theoretical and experimental investigation of the Andersen Mark II Cascade Impactor suggests that the size distribution measurements obtained during impactor tests are very dependent on which Mark II impactor is used (Stein and Olson, 1997). It was determined that these differences are due to differences in the diameters of the jets among Mark II impactors.

Particle size distribution measurements are almost always used as part of the acceptance testing for pharmaceutical aerosols such as metered dose inhalers (MDIs). The Mark II impactor is often used to make these size distribution measurements. Since cascade impactor tests are often used to accept or reject lots of manufactured aerosols, it is critical to appropriately interpret the results obtained from cascade impactor tests. This task is complicated by the fact that the cascade impactors used to set the size distribution acceptance specifications for a product are often different than the cascade impactors actually used to clear product for sale. Specifications are usually set based on cascade impactor tests run in a research and development (R&D) laboratory during the development and stability phase of the product development cycle. Product clearance tests, which must meet the R&D generated specifications, are often performed at a separate quality control laboratory using different cascade impactors. Therefore, it is important to obtain consistent size distribution measurements regardless of which cascade impactor is used.

In the previous examination of the Andersen Mark II impactor, a stable oil droplet aerosol was used to compare the results obtained with multiple Mark II impactors (Stein and Olson, 1997). This test aerosol was ideal for comparing size distribution measurements of multiple Mark II impactors sampling an identical aerosol, but it was not representative of the sampling of a dynamic MDI aerosol. The purpose of this paper is to determine if consistent results are obtained when three different Mark II impactors sample various MDI products. The previous examination included theoretically calculated size distributions for real Mark II impactors that did not meet the manufacturer's internal specifications. This paper presents theoretical calculations for various hypothetical Mark II impactors that meet the manufacturer's specifications. These calculations provide insight into the limits of precision of Mark II impactors when only impactors that conform to the manufacturer's specifications are used.

2. Material and methods

The performance of various Mark II impactors was investigated theoretically and experimentally. For the theoretical investigation, calculations were made to assess the influence that differences in jet diameters have on stage cutpoints and on size distribution measurements. Experimental measurements of three MDI products were also taken using three different Andersen impactors. The size distribution measurements obtained with the three Andersen impactors were compared.

2.1. Theoretical investigation of Andersen Mark II cascade impactors

A theoretical exercise was undertaken to assess the impact that differences in the diameter of the jets have on size distribution measurements. Stage cutpoints were calculated for the stages based on jet diameter values. For this exercise, only jet diameters within the manufacturer's specifications were considered. These specifications are nonbinding internal specifications implemented by the manufacturer that apply only to Mark II impactors purchased after approximately 1995.

These specifications are not published in the Mark II operating manual, but have been provided freely by the manufacturer in telephone conversations. These specifications are summarized in Table 1. Stage cutpoints were calculated for Andersen Mark II impactors at the upper and lower limits of the manufacturer's jet diameter specifications.

$$\mathrm{Stk} = \frac{\rho_0 d_a^2 U C_c}{9\eta D_j} \quad (1)$$

In order to calculate stage cutpoints it was necessary to examine the equation defining the Stokes number that governs inertial impaction, where Stk is the Stokes number, ρ_0 is unit density (1.0 g/cm^3), d_a is the aerodynamic particle diameter, U is the jet velocity, C_c is the Cunningham slip correction and is a function of particle size, η is the viscosity of the air, and D_j is the jet diameter.

The collection efficiency for a given impactor stage is a function of the Stokes number and can be numerically or experimentally determined (Marple, 1970; Rader and Marple, 1985). The most descriptive value of an impactor stage is the Stk_{50}. This is the Stokes number at which 50% of the particles impact and are collected. The aerodynamic cutpoint of a stage, d_{a50}, is the particle diameter at which $\mathrm{Stk} = \mathrm{Stk}_{50}$. The Stk_{50} of a given impactor stage depends on the Reynolds number of the flow and the physical dimensions of the stage such as the jet diameter, the distance between the back of the impaction stage and the impaction plate, the length of the jet, and the number of jets. Previous impactor research (Marple, 1970; Rader and Marple, 1985) has shown that Stk_{50} is insensitive to changes in jet diameter and Reynolds' number of the magnitude that we are interested in when comparing two similar impactor stages (such as Stage 3 from two different Andersen impactors). As a result, Stk_{50} was assumed to be constant for identical stages of each of the impactors tested. However, the value of Stk_{50} for Stage 3 is certainly different than the value for other stages (such as Stage 4) due to differences in the stage geometry and Reynolds number.

Table 1
Jet diameter specifications for stages of Mark II cascade impactors sold since approximately 1995[a]

Stage #	Manufacturer's jet diameter specification
0	0.0994–0.1014″
1	0.0734–0.0754″
2	0.0355–0.0365″
3	0.0275–0.0285″
4	0.0205–0.0215″
5	0.0130–0.0140″
6	0.0095–0.0105″
7	0.0095–0.0105″

[a] These specifications are not published in the Mark II operating manual, but were provided freely by the manufacturer in telephone conversations.

$$d_{a50} = \sqrt{\frac{9\mathrm{Stk}_{50}\eta\pi D_j^3 N}{4\rho_0 Q C_c}} \quad (2)$$

By rearranging Eq. (1) and substituting for jet velocity it is possible to solve for the aerodynamic cutpoint, d_{a50}, of a stage. It is necessary to iteratively solve for d_{a50}, because of the dependence of slip correction, C_c, on particle diameter. In this equation Q is the total flow rate through the impactor stage and N is the total number of jets on the impactor stage. Notice that two impactors with exactly the same Stk_{50} will have different aerodynamic cutpoints if they have different jet diameters, flow rates, or number of jets.

The stage cutpoints calculated for impactors with jet diameters at the edge of the specifications were used to predict the stage deposition characteristics for five hypothetical impactors. The impactors were assumed to sample a lognormally distributed aerosol and also to have perfectly sharp stage cutoffs. The mass that would collect on each stage was calculated by determining the percent of mass for the assumed lognormal size distribution with aerodynamic diameters between the stage cutpoint and the previous stage cutpoint. It is assumed, for example, that Stage 4 will collect all of the particles smaller than the Stage 3 cutpoint but larger than the Stage 4 cutpoint for a given size distribution. This is a simple statistical calculation based on the properties of a lognormal aerosol.

Table 2
Stage cutpoints (μm) calculated for three Mark II impactors used for size distributions of various MDI products[a]

Stage #	Reported cutpoint	Cutpoint		
		Serial # 2589	Serial # 2658	Serial # 3077
0	9 (0.0994–0.1014″)	8.84 μm (0.0992″)	9.07 μm (0.1009″)	9.07 μm (0.1009″)
1	5.8 (0.0734–0.0754″)	5.79 μm (0.0743″)	5.63 μm (0.0730″)	5.87 μm (0.0750″)
2	4.7 (0.0355–0.0365″)	4.72 μm (0.0361″)	4.88 μm (0.0369″)	4.64 μm (0.0357″)
3	3.3 (0.0275–0.0285″)	3.41 μm (0.0286″)	3.45 μm (0.0288″)	3.23 μm (0.0276″)
4	2.1 (0.0205–0.0215″)	2.16 μm (0.0214″)	1.99 μm (0.0203″)	2.26 μm (0.0220″)
5	1.1 (0.0130–0.0140″)	1.26 μm (0.0147″)	1.10 μm (0.0135″)	1.07 μm (0.0133″)
6	0.7 (0.0095–0.0105″)	0.60 μm (0.0091″)	0.64 μm (0.0095″)	0.71 μm (0.0101″)
7	0.4 (0.0095–0.0105″)	0.39 μm (0.0099″)	0.38 μm (0.0097″)	0.39 μm (0.0099″)

[a] The cutpoints were calculated using Eq. (2) and the average jet diameters which are indicated in parenthesis.

2.2. Experimental investigation of three Andersen Mark II cascade impactors

Three Andersen Mark II impactors were selected for examination during this study. The serial numbers for these impactors are # 2589, # 2658, and # 3077. Jet diameter measurements and cutpoint calculations for these three impactors were reported in the previous paper and are summarized in Table 2. Jet diameters were measured using a Measurescope MM-22 microscope (Nikon, Melville, NY) equipped with a Quadra-Chek 2000 (Metronics, Manchester, NH) at × 50 magnification. The position of four points on the perimeter of the jet were marked. The Quadra-Chek then calculated the best-fit circle for the four data points using a least-squares technique and output the diameter of this best-fit circle (see Stein and Olson, 1997, for further details). The stage cutpoints listed in Table 2 were calculated using Eq. (2) and jet diameter measurements. It was noted in the previous paper that the irregularity of some of the jets measured is a potential source of errors in the cutpoint calculations.

During the previous study, jet diameters were measured for 14 Andersen Mark II impactors. Every impactor measured was determined to have between one and five stages that failed the manufacturer's jet diameter specifications. Some of the impactors measured were purchased prior to the manufacturer's adoption of the internal jet diameter specifications. The three impactors used in this study, Andersens # 2658, # 2589, and # 3077, had four, four, and one stage that failed the specifications, respectively. The first two impactors were purchased prior to the manufacturer's adoption of the jet diameter specification. All three impactors had been used extensively in testing. The previous investigation did not show any evidence that the jet diameters were affected by the age or usage of the impactor (Stein and Olson, 1997).

Tests were performed on three MDI products: (1) QVAR™ (50 μg/dose); (2) Beclovent™ (42 μg/dose); and (3) Flixotide™ (250 μg/dose). The main reason that these three products were selected was to examine aerosols of various sizes. QVAR™ has a mass median aerodynamic diameter (MMAD) of approximately 1 μm, Flixotide™ approximately 2.5 μm, and Beclovent™ approximately 4 μm. For each product tested, a single MDI vial was used. Each product was tested nine times: three times with each impactor. The same USP induction port was used for all of the tests. All tests were five-dose assays. The impaction plates of the Andersen impactor were not coated for any of the tests.

The drug collected on the valve stem, mouthpiece, USP induction port, and Andersen impaction plates was dissolved by rinsing each component with a known volume of solvent. Each of these samples was assayed using an HPLC (Waters™ LCI plus, Waters, Milford, MA) with a

UV detector measuring at 238 nm. The mobile phase was 60% acetonitrile in ultra-pure water and a Supelcosil™ LC-18 column (150 × 4.6 mm, 5 μm particle size; Supelco, Bellefonte, PA) was used.

3. Results

3.1. Theoretical investigation of Andersen Mark II cascade impactors

The stage cutpoints were calculated for five hypothetical Andersen impactors with stages that meet the manufacturer's jet diameter specifications. The stage cutpoints and jet diameters for these hypothetical impactors are summarized in Table 3. The stage cutpoints listed in Table 3 were calculated using Eq. (2). The stage cutpoints in Table 3 were used to predict the stage deposition characteristics of each impactor when sampling a given lognormal aerosol. In order to perform the calculations, the following assumptions were made: (1) each impactor was assumed to sample a perfectly lognormal aerosol; (2) the stage cutoffs were assumed to be perfectly sharp (i.e. they collect no particles smaller than the cutpoint and all particles larger than the cutpoint); and (3) the interstage losses were ignored. The mass that would collect on a given stage was calculated by determining the percent of mass for a given lognormal size distribution with aerodynamic diameters between the stage cutpoint and the previous stage cutpoint.

The assumption that the stages have perfectly sharp stage cutoffs introduces some error into the stage deposition calculations. In reality, a small fraction of particles larger than the Stage 3 cutpoint penetrates through Stage 3 and collects on subsequent stages. However, this is counteracted by the fact that Stage 3 collects a small fraction of particles smaller than the Stage 3 cutpoint. The net effect of this is small for impactors, such as the Andersen Mark II, that have relatively sharp stage cutoffs. The collection efficiency curves for the stages of the Mark II have been reported elsewhere (Mitchell, et al., 1988; Vaughan, 1989).

Stage deposition characteristics were calculated for the five hypothetical Mark II impactors sampling a lognormal aerosol with an MMAD of 2.40 μm and a geometric standard deviation (σ_g) of 1.70. Based on these calculations, the mass collected on Stage 4 was predicted to vary from 27.7 to 37.3% of the total sampled mass depending on which impactor was used (Stage 3 would vary from 14.5 to 19.9%, Stage 5 from 28.4 to 37.3%, Stage 6 from 4.1 to 8.0%, etc.). In the previous paper, the theoretical calculations were observed to overestimate the range in amount of drug collected on a given stage by about 20–30%. As a result, the theoretical calculations were empirically corrected. This was done by adjusting each predicted stage deposition value so that it was 25% closer to the average value of that stage for the five impactors. In this way the range of values was reduced by 25%.

The empirically corrected theoretical calculations are summarized in Fig. 1. The differences in the amount collected on each stage in Fig. 1 are representative of what one would expect to find for actual size distribution measurements made with Mark II impactors that meet the manufacturer's specifications. Notice that the mass collected on Stage 4 is expected to vary from 28.9 to 36.1% of the total sampled mass for the five hypothetical Andersens (Stage 3 is expected to vary from 15.2 to 19.2%, Stage 5 from 29.5 to 36.2%, Stage 6 from 4.6 to 7.5%, etc.).

Fig. 1 illustrates that there can be large differences in the amount of drug collected on the stages of various Mark II impactors—even for impactors that meet the manufacturer's specifications. If stages are used that do not conform to the manufacturer's jet diameter specifications, even larger differences in the amount of drug collected on the various stages should be expected.

These calculations illustrate how relatively small differences in the diameter of the jets on impactor stages can cause moderate differences in the cutpoints of 'identical' impactor stages (Table 3). These moderate differences in cutpoints can cause large differences in the amount of drug that collects on the stages of the impactor during size distribution measurements (Fig. 1). Similar calcu-

lations could be made for other types of cascade impactors and similar conclusions would most likely be reached. It is not reasonable to expect that different impactors of the same type will have exactly the same stage cutpoints. It is, therefore, not practical to analyze cascade impactor data on a stage-by-stage basis, particularly when multiple cascade impactors are used for measurements. Grouping stages together generally reduces the differences in size distribution measurements from impactor to impactor, but it does not eliminate these differences (Stein and Olson, 1997). Stage groupings can actually increase the magnitude of the differences in size distribution measurements among impactors depending on the stages that are grouped together, the size distribution of the aerosol being measured, and the cutpoints of the impactors being used.

3.2. Experimental investigation of three Andersen Mark II cascade impactors

Experiments were performed on three different MDI products using three different Andersen Mark II cascade impactors. A single vial of each product was tested three times with each of the three impactors being investigated. The results are presented on a product by product basis.

3.2.1. QVAR™, 50 μg/dose

The results from the tests using a QVAR™ HFA-134a beclomethasone dipropionate MDI are summarized in Table 4. This CFC-free MDI was manufactured by 3M Pharmaceuticals and is a solution product. The values listed under 'Jet' in Table 4 represent the amount of drug that collected on the Stage 0 jet plate during the tests. The values listed under 'Stage 0' indicates the amount of drug that collected on the Stage 0 impaction plate.

During the tests, the average throat deposition (in μg/dose) for the three impactors varied from 11.7 to 14.1 μg/dose. Despite the random variability in the amount collecting on the valve stem, mouthpiece, and throat, there are statistically significant differences in the amount collected on Stages 4, 5, 6, and 7 for the three impactors. The differences are particularly large for Stages 5 and 6—the stages that collected the most mass for this MDI product. The fact that there were not statis-

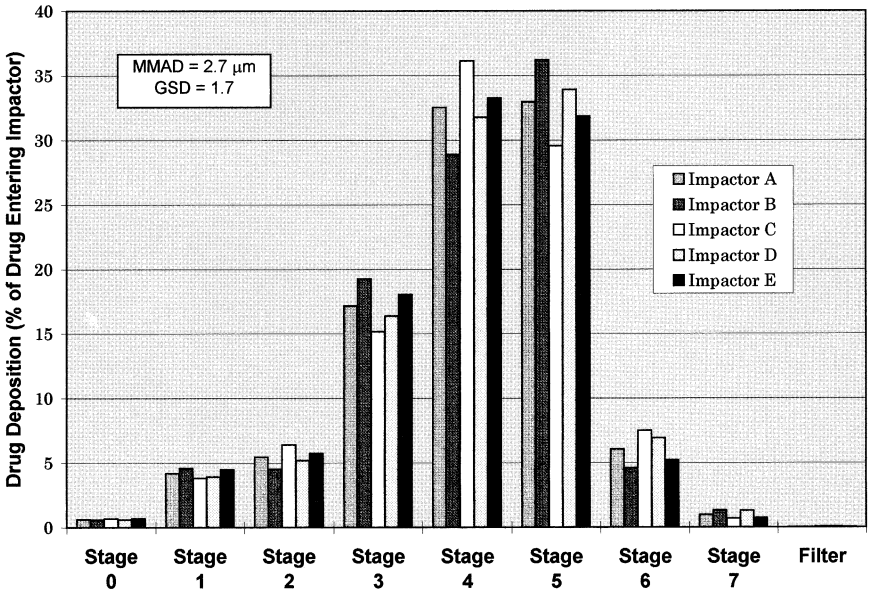

Fig. 1. Predicted size distribution measurements for five hypothetical Mark II cascade impactors sampling an identical lognormal size distribution. The predictions were empirically adjusted based on the findings of Stein and Olson (1997).

Table 3
Stage cutpoints (μm), calculated for five hypothetical Mark II impactors (Imp. A–E) that meet the manufacturer's jet diameter specifications[a]

Stage #	Reported cutpoint	Cutpoint				
		Imp. A	Imp. B	Imp. C	Imp. D	Imp. E
0	9 μm (0.0994–0.1014″)	9.00 μm (0.1004″)	9.15 μm (0.1014″)	8.84 μm (0.0994″)	9.15 μm (0.1014″)	8.84 μm (0.0994″)
1	5.8 μm (0.0734–0.0754″)	5.80 μm (0.0744″)	5.66 μm (0.0734″)	5.93 μm (0.0754″)	5.93 μm (0.0754″)	5.66 μm (0.0734″)
2	4.7 μm (0.0355–0.0365″)	4.70 μm (0.0360″)	4.81 μm (0.0365″)	4.59 μm (0.0355″)	4.81 μm (0.0365″)	4.59 μm (0.0355″)
3	3.3 μm (0.0275–0.0285″)	3.30 μm (0.0280″)	3.20 μm (0.0275″)	3.40 μm (0.0285″)	3.40 μm (0.0285″)	3.20 μm (0.0275″)
4	2.1 μm (0.0205–0.0215″)	2.10 μm (0.0210″)	2.18 μm (0.0215″)	2.01 μm (0.0205″)	2.18 μm (0.0215″)	2.01 μm (0.0205″)
5	1.1 μm (0.0130–0.0140″)	1.10 μm (0.0135″)	1.03 μm (0.0130″)	1.16 μm (0.0140″)	1.16 μm (0.0140″)	1.03 μm (0.0130″)
6	0.7 μm (0.0095–0.0105″)	0.70 μm (0.0100″)	0.75 μm (0.0105″)	0.64 μm (0.0095″)	0.75 μm (0.0105″)	0.64 μm (0.0095″)
7	0.4 μm (0.0095–0.0105″)	0.40 μm (0.0100″)	0.37 μm (0.0095″)	0.43 μm (0.0105″)	0.43 μm (0.0105″)	0.37 μm (0.0095″)

[a] The cutpoints were calculated using Eq. (2) and the hypothetical jet diameters which are indicated in parenthesis.

Table 4
The amount of drug collected on individual stages of three Mark II impactors during testing of the QVAR™ HFA-134a beclomethasone dipropionate MDIs[a]

	Serial # 2589 (μg/shot)	Serial # 2658 (μg/shot)	Serial # 3077 (μg/shot)
Valve stem	2.2 ± 0.1	2.2 ± 0.2	2.2 ± 0.2
Actuator	10.7 ± 0.6	9.7 ± 0.2	10.1 ± 0.5
USP throat	13.3 ± 0.7	12.2 ± 0.6	12.4 ± 0.6
Jet Stage	0.1 ± 0.0	0.2 ± 0.3	0.1 ± 0.0
Stage 0	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Stage 1	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Stage 2	0.1 ± 0.0	0.1 ± 0.0	0.1 ± 0.0
Stage 3	0.2 ± 0.0	0.2 ± 0.0	0.2 ± 0.0
Stage 4	0.8 ± 0.2	1.4 ± 0.1	0.9 ± 0.0
Stage 5	5.3 ± 0.3	7.8 ± 0.2	7.9 ± 0.1
Stage 6	8.9 ± 0.6	6.8 ± 0.3	6.7 ± 0.2
Stage 7	2.5 ± 0.2	3.3 ± 0.1	3.5 ± 0.1
Filter	3.5 ± 0.5	3.4 ± 0.3	3.6 ± 0.2

[a] The average and standard deviation of three tests are given for each impactor.

tically significant differences in the amount of drug that collected on Stages 0–3 is most likely due to precision limitations of the test method and the minimal amount of drug collected on these stages for this particular test aerosol. Had sufficient drug collected on these stages, they too would likely have shown statistically significant differences.

The results in Table 4 are graphically presented in Fig. 2. In this figure, the stage deposition values were normalized as a percent of the total drug that entered into the cascade impactor. This al-

lows the best comparison of the impactors since it eliminates variability in stem, mouthpiece, and throat holdup. The error bars in Fig. 2 represent the standard deviations of the measurements with each impactor. Notice that the measurements were very repeatable (as indicated by the standard deviations) for a given impactor. However, from one impactor to the next, large differences were observed.

3.2.2. *Flixotide™, 250 μg/dose*

Flixotide™ is a CFC suspension MDI manufactured by Glaxo Wellcome. Results from size distribution measurements of 250 μg/dose Flixotide™ (Lot WM1WMD) are summarized in Fig. 3. Throat deposition during the tests ranged from 83.2 to 99.1 μg/dose. This variability will cause some variability in the amount of drug collected on each stage of the Andersen impactor during the tests. Despite this random variability in the stem, mouthpiece, and throat deposition, there were statistically significant differences observed in the amount of drug collecting on Stages 2, 4, 5, and 6. While consistent measurements were obtained with a single Mark II impactor, there were large differences in the amount of drug collecting on each stage for the three different impactors tested. The differences in the amount of drug collected on Stages 4 and 5 are particularly large. These measurements demonstrate that the results of size distribution measurements of Flixotide™ are strongly dependent on which Andersen Mark II impactor is used.

3.2.3. *Beclovent™, 42 μg/dose*

Beclovent™ is a CFC suspension MDI manufactured by Glaxo Wellcome. It was examined because it has a larger particle size distribution than the other two products tested. The results from size distribution measurements of 42 μg/dose Beclovent™ (Lot 6ZP0130) are summarized in Fig. 4. The throat deposition ranged from 23.9 to 26.5 μg/dose. There are statistically significant differences among the impactors in terms of the amount of drug collected on Stages 2, 3, 5, and 7.

The significant amount of drug collected on the filter stage for the Beclovent™ tests (Fig. 4) indicates that there is probably particle bounce occurring on the stages of the Andersen impactor. When a particle bounces, it often re-enters the

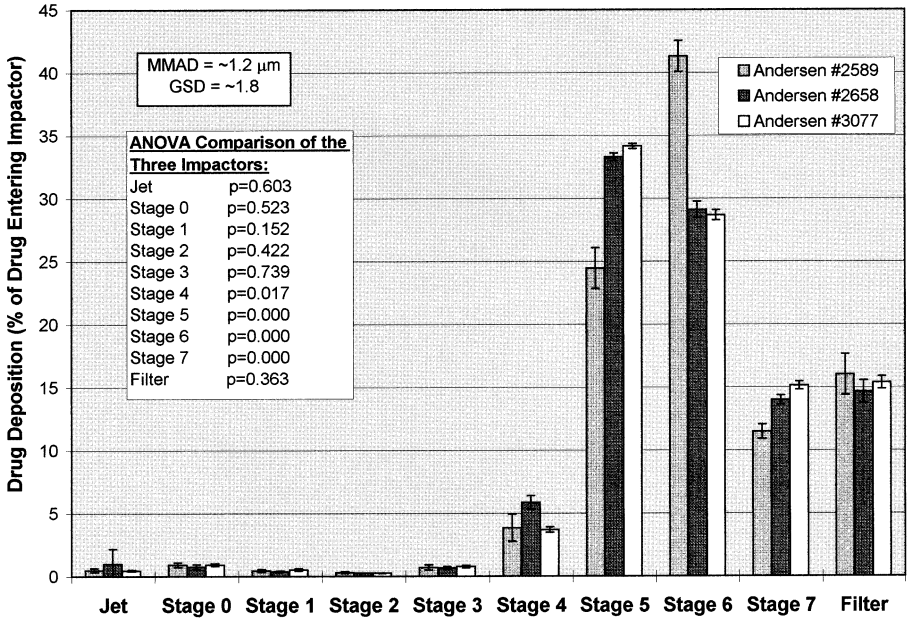

Fig. 2. Measurements of a QVAR™ HFA-134a beclomethasone dipropionate MDI with three different Mark II cascade impactors. The error bars indicate standard deviations of three measurements.

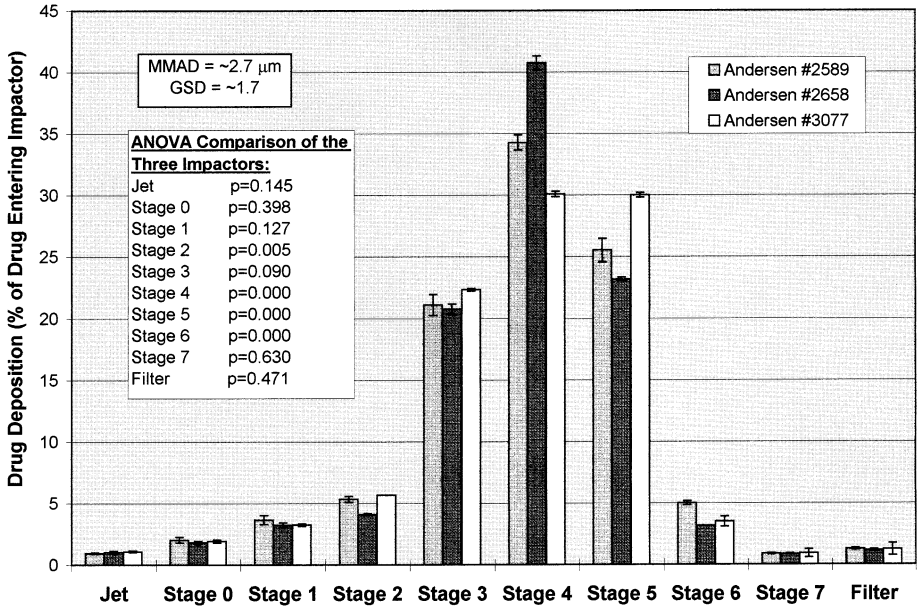

Fig. 3. Measurements of a Flixotide™ MDI with three different Mark II cascade impactors. The error bars indicate standard deviations of three measurements.

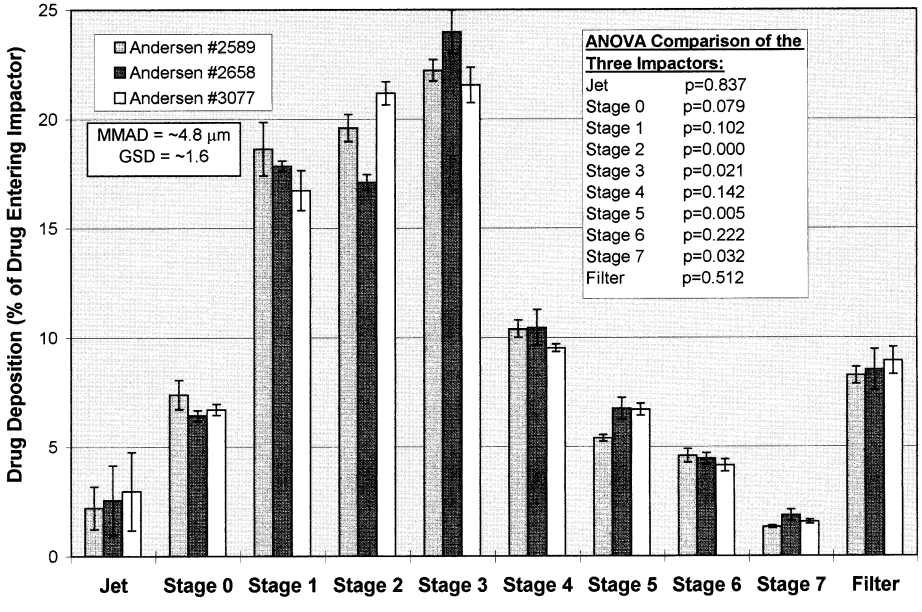

Fig. 4. Measurements of a Beclovent™ MDI with three different Mark II cascade impactors. The error bars indicate standard deviations of three measurements.

airflow and impacts on the next stage. Because jet velocities generally increase on subsequent stages of an impactor, the particle will have more kinetic energy and will be even more likely to bounce

when impacting on the next stage. As a result, a particle that bounces off one stage of an impactor often bounces off of all the subsequent stages until it collects on the filter stage. This causes the amount of material collected on the filter stage to be erroneously high (Dzubay, et al., 1976). This appears to have occurred during our Beclovent™ tests.

Particle bounce leads to erroneous estimates of the actual particle size distribution. The amount of bounce that occurred during our testing of Beclovent™ was quite consistent from test to test and did not appear to depend on which impactor was used. While these errors lead to a misrepresentation of the actual particle size distribution, they do not necessarily preclude the use of the Andersen impactor as a quality control device used to detect differences among Beclovent™ MDIs. Perhaps of greater concern than bounce errors are the errors in the measured size distributions due to variability in the Andersen jet diameters. Unlike particle bounce errors, these errors depend on which instrument is used and, therefore, will not be consistent from one test to the next.

4. Conclusions

Three MDI products were sampled using three different Andersen Mark II cascade impactors. Measurements of the same MDI were very consistent for a given Andersen impactor, but large differences were observed in measurements of the same MDI with different impactors. A previous study (Stein and Olson, 1997) showed that the differences in performance among Andersen impactors are due to jet diameter differences among impactors. Since it is usually not practical to use the same cascade impactor for all quality control tests of MDIs, impactor to impactor differences will inevitably be a source of uncontrollable variation in MDI size distribution measurements.

Theoretical calculations indicate that large differences in measured size distributions should be expected from impactor to impactor—even for impactors that meet the manufacturer's jet diameter specifications. These data suggest that it is impractical to analyze size distribution data on a stage by stage basis—even when cascade impactors that conform to the manufacturer's specifications are used. It is important to take into consideration the limited precision of cascade impactors, such as the Andersen Mark II, when analyzing the size distribution measurements that they provide.

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