Particle Size Distribution of a Suspension Aerosol Using Andersen and Marple-Miller Cascade Impactors

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INTRODUCTION

The aerodynamic diameter of the particles is a critical parameter in characterization of suspension aerosols or metered-dose inhalers (MDI). Aerodynamic size distribution defines the manner in which a drug deposits during inhalation or is delivered to the most effective site(s) of the lung (1,2). Andersen cascade impactor (ACI) or equivalent is recommended by USP to determine aerodynamic particle size distribution (3). The use of the ACI is labor intensive and has bias towards a lower Mass Median Aerodynamic Diameter (MMAD) resulting from high inter-stage wall losses and particle bounce on impaction discs (4). The Marple-Miller Impactor (MMI) was reported to provide particle size distribution with relatively low interstage losses and convenient operation (5). The mass distribution refers to the estimated amounts of the drug particles deposited at various sections of the apparatus. The particle size distribution refers to the amounts of the drug particles estimated at various predetermined cut-off stages. This study evaluates these two multistage cascade impactors for the actual aerodynamic sizing and total mass distribution of a peptide drug in an aerosol suspension. In addition, changes in the particle size distribution of the canisters exposed to high temp./RH were analyzed by both the impactors.

MATERIALS AND METHODS

A completely characterized peptide drug reference standard, and five suspension aerosol canisters (125 μg of drug/spray) from Lot A manufactured by Abbott Laboratories, North Chicago, IL., were used in this study. The reagents and chemicals of ACS or HPLC grade were used throughout the study. All analyses were performed at ambient temperature.

The Marple-Miller Impactor, MMI (Model 150, MSP Corporation, Minneapolis, MN) and the Andersen Cascade Impactor, ACI (Model Mark II, 1 ACFM Nonviable Particle Sizing Sampler; Andersen Samplers Inc., Atlanta, GA) were used to delineate particle size distribution of the aerosol. An induction port (throat) as described in USP (1) was used for both impactors. Five aerosol canisters from Lot A were tested by the impactors in a random sequence.

The ACI consists of 8 stages, collection plates and a final filter (Whatman glass microfibre filter, 8 cm diameter; Cat. No. 1820-080). The stage cut-off diameters are 9, 5.8, 4.7, 3.3, 2.1, 1.1, 0.65 and 0.43 μm at stages 0 to 7, respectively (6). The valve priming of each canister was performed by shaking the canister vigorously for 30 seconds and dispensing 2 sprays to waste. Ten shots from each of the aerosol canisters were discharged into the apparatus. Samples were drawn through the impactor under a 28.3 L/min. stream of air provided by a vacuum pump and monitored by a calibrated flow meter. The fractions of sized particles collected at various sites of the apparatus were separately recovered in methanol and determined by HPLC.

The MMI is a 5-stage cascade impactor designed to measure the particle sizes produced by the MDI. The stage cut-off diameters are 10, 5, 2.5, 1.25 and 0.625 μm. The valve priming of each canister was performed as described previously. Ten shots were discharged from each canister with an actuator under a 30 L/min. stream of air monitored by a calibrated flow meter (Omega Engineering, Inc., Model FL-3663ST). The smaller particles pass through the actuator and artificial throat and are collected by the five stage impactor with the cut-off diameters, and finally on a Gelman 5 mm Metricel VM-1 filter (37 mm diameter, Cat. No. 60714), without a pad. The drug collected from various stages of the impactor and in sites outside the instrument (stem, actuator, coupler, and port) was recovered in methanol and determined by the HPLC. A data reduction program, IMPACTORPLOT (Nephele Enterprises, White Bear Lake, MN), was used for processing the data generated by the cascade impactors. MMAD, Geometric Standard Deviation (GSD) and the fine particle size fraction (Cum. % <4.7 μm for the ACI; and <5 μm for the MMI) were calculated from the drug collected at various sites of the apparatus. The results obtained from both the impactors were compared using the Wilcoxon Signed Rank test (9).

Effect of Temp/RH on Particle Size Distribution

Two suspension aerosol canisters were used for each experiment. One aerosol container from Lot B, and one container from Lot C were stored for 4 months at 40°C/75% and 40°C/85% RH,

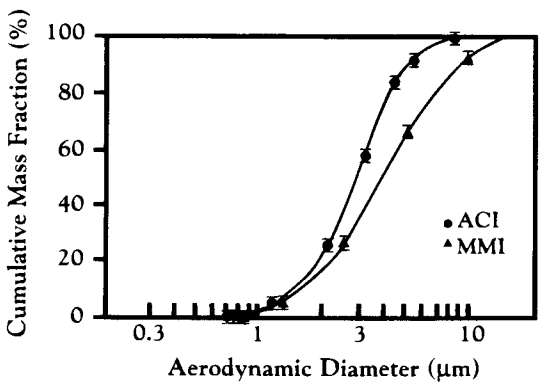

Fig. 1. Cumulative Mass Distribution Curves (N = 5) from a Peptide Suspension Aerosol, Lot A for ACI and MMI.

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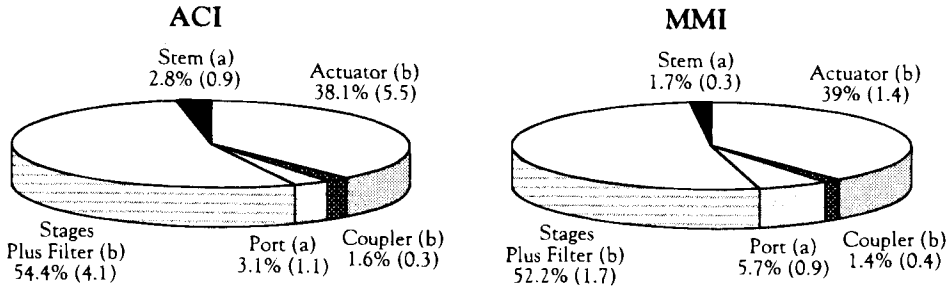

Fig. 2. Mass Distribution in ACI and MMI. Figures in parenthesis indicate standard deviation. The labels indicated by (a) are significantly different at $P \leq 0.5\%$, and labels indicated by (b) are not significantly different at $P \leq 0.5\%$.

respectively. Controls were stored at ambient temp/RH. Particle size distributions of these two treatments were analyzed by both of the impactors.

Determination of Drug by HPLC

The HPLC system consisted of a Waters 6000A pump, WISP injector, a multiwavelength detector (Waters Associates, Milford, MA) and an electronic integrator/recorder (SP-4400, Spectra Physics). An Apex ODS, 5 μm, 150 mm, 4.6 mm i.d., analytical column (Jones Chromatography USA, Inc.) was used. The mobile phase contained 70% (v/v) of aqueous monobasic ammonium phosphate solution (0.087 M, pH 6.5, adjusted with ammonium hydroxide) and 30% of acetonitrile. The flow rate was ~2.0 mL/min. The absorbency range was 0.02 to 0.05 Absorbance Units Full Scale (AUFS) at 220 nm and the injection volume was 30 μl. The standard and sample preparations were injected in duplicate, and the average peak area response of the drug was used to estimate the drug concentration. The retention time of the drug was approximately 4 minutes. The drug contents from the samples were read against a standard curve.

RESULTS AND DISCUSSION

Particle-size Distribution

The particle mass distribution data and mean cumulative mass percentage obtained on 5 cans of the suspension aerosol for the ACI and the MMI are shown in Fig. 1. The variation in particle distribution could be due to the differences in inter-stage wall losses and particle-bounce characteristics of the impactors and/or due to differences in the capability of the impactors to resolve information (i.e., 8 stages versus 5 stages). About 54.4% mass was deposited in the stages and filter of the ACI, which is comparable to 52.2% obtained for the MMI (Fig. 2). Similarly, 47.8% of drug amount was deposited on the sites outside of the MMI stages (stem, actuator, coupler and port) compared to 45.6% from the ACI experiments. Wilcoxon Signed Rank test analysis showed that the mass distribution

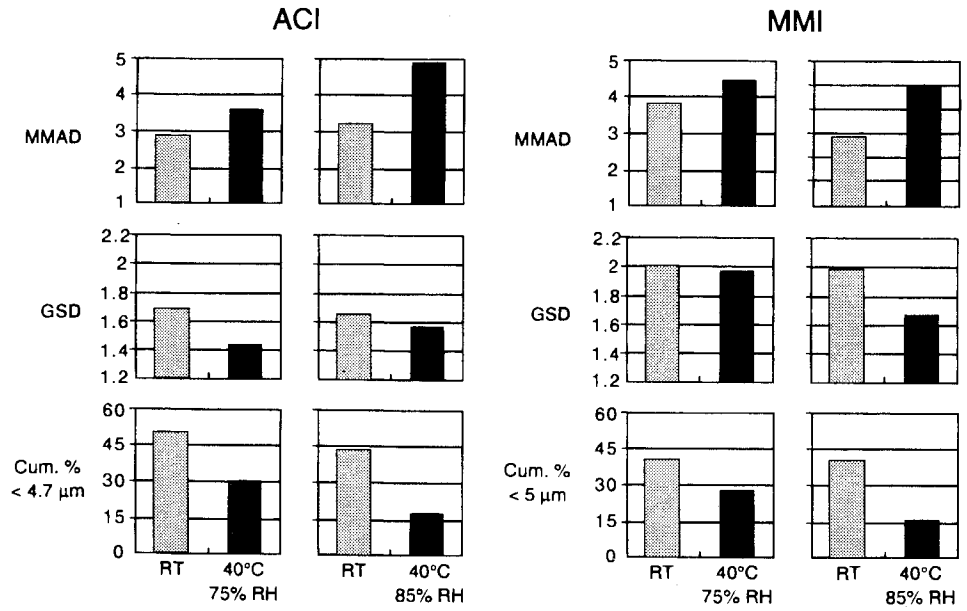

Fig. 3. Particle Size Distribution in ACI and MMI of canisters stored at RT and High Temperature/ High Humidity. Canisters from Lot B and C subjected to 40°C/75% RH and 40°C/85% RH, respectively.

between the ACI and the MMI significantly differed at $P \leq 0.5\%$ in the stem and port locations. The mass distribution between the ACI and the MMI at actuator, coupler and stages plus filter were not significantly different at $P \leq 0.5\%$ level.

MMAD, GSD, and Cumulative % < Size Values

The MMAD, GSD and the Cumulative % < size (fine particle fraction) values were determined using mass distributions of impaction results. The results showed good reproducibility within each impactor. The particle distribution in the ACI averaged 2.9 ± 0.16 μm (1.8 ± 0.06) and 44.7 ± 3.86% respectively, for the MMAD (GSD) and the "Cum. % < 4.7 μm" values for the 5 cans. The particle distribution in the MMI averaged 4.0 ± 0.17 μm (1.95 ± 0.05) and 34.6 ± 1.89%, respectively for the MMAD (GSD) and the "Cum. % < 5 μm". The mean values of the MMAD (GSD) were lower in the ACI compared to the MMI. The cumulative % of fine particle fraction in the ACI was higher compared to the MMI. These results may be explained by higher interstage wall losses in the ACI compared to the MMI (5), which could result in overestimation of the fine particle fractions (4).

Microscopic analysis of peptide suspension aerosol canisters, which were exposed to high temp./RH conditions (40°C/75–85%RH) showed aggregates and/or changes in particle size and morphology (*unpublished*). The canisters subjected to higher temp./RH showed an increase in the MMAD with a concurrent decrease in the GSD and fine particle fraction (Cum. % < Size) values compared to controls stored at ambient temp./RH (Fig. 3). The data from both the impactors showed a similar trend. The particle distribution showed significant changes, especially skewed towards larger particle size, in response to humidity. Similar results were obtained from aerosol canisters exposed to higher temperatures/RH (7). It may be hypothesized that moisture may enter the canister through the gasket around the valve stem and the gasket between the valve body and metal container (7). However, the specific mechansim(s) of moisture entry into the aerosol canister is unclear. Moisture entering the aerosol canisters can cause a decrease in the number of smaller particles and a concurrent increase in the number of larger particles by the Ostwald ripening process (8). The rate of aggregation of particles depends on the temperature and relative humidity of the storage conditions (7).

In conclusion, supportive data is provided to use either the ACI or the MMI for the size analysis of a suspension aerosol. The total mass distribution inside and outside of the instrument was similar in both impactors. The ability of impactors to generate reproducible particle size distribution data and reliably detect changes that affect product performance is confirmed. The impaction results are used to monitor the batch control (inter-lot consistency) of the manufacturing process and aerosol stability (particle size) over time. Hence, absolute equivalency in the impaction results between the two impactors is not critical. The MMI, with the ease of operation and reduced analysis time, is the preferred device for this application.

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