Cascade Impaction Testing of Microchamber® Spacer Device with Two Medications

A TECHNICAL REPORT

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Introduction:

The MicroChamber® is a non-valved reservoir device, often designated as a spacer. The reservoir is approximately 10.5 cm in length, 4.5 cm in diameter, cylindrical, with a calculated volume of approximately 125 cc's exclusive of the mouthpiece. An integral tubular mouthpiece contains an open mesh baffle. A flexible oval opening at the end opposite the mouthpiece accepts the pharmaceutical manufacturer's MDI mouthpiece/actuator. A diagram of the MicroChamber® spacer is given in Figure 1.

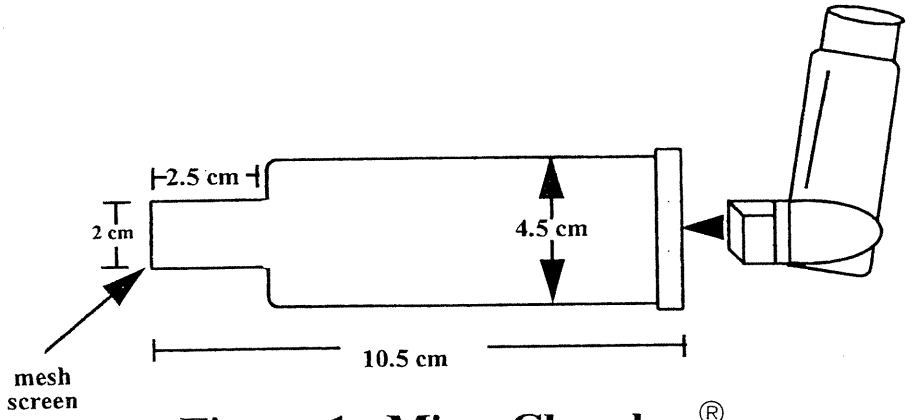


Figure 1. MicroChamber®

Purpose of Project:

The purpose of the project was to provide particle size distribution data using a cascade impaction technique, for the MicroChamber®, with CFC-formulated albuterol (PROVENTIL®) and HFA-formulated albuterol (PROVENTIL® HFA).

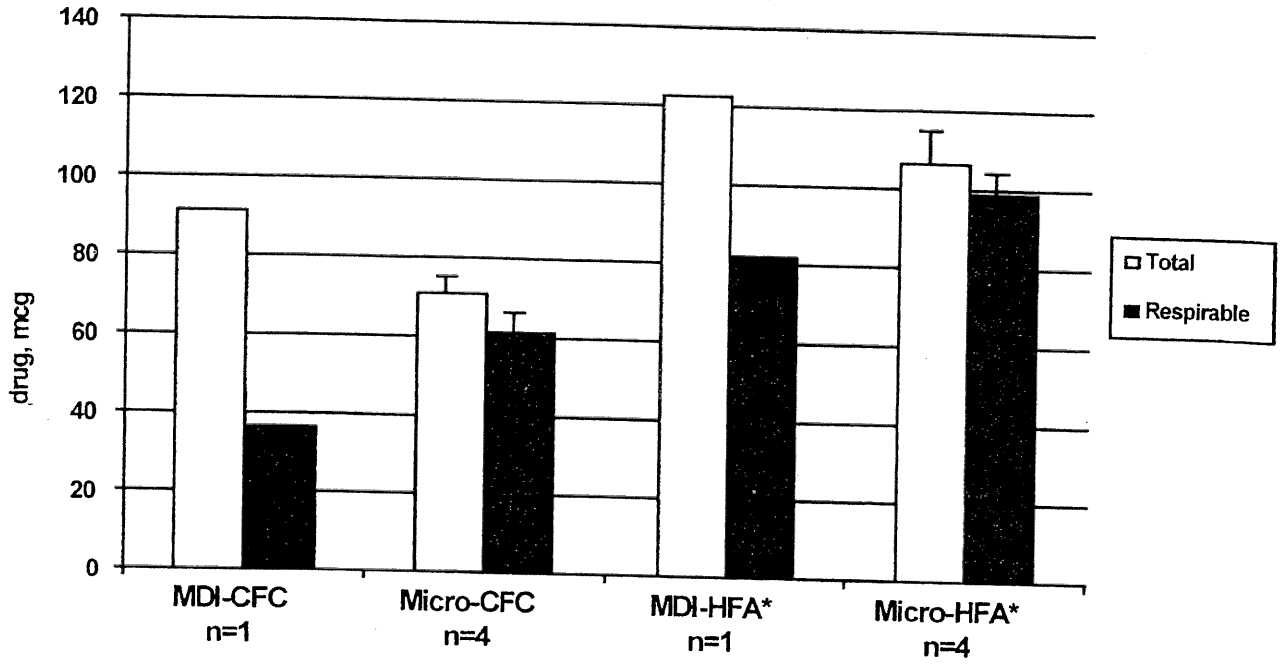
Methods:

The MicroChamber® was tested with each of two metered dose (MDI) medications: PROVENTIL® brand of albuterol (CFC formulation, Schering Corp.) and PROVENTIL® HFA brand of albuterol (HFA-formulation, Key Pharmaceuticals). Each actuation of PROVENTIL® delivers 90 µg of albuterol from the mouthpiece, and the canister is rated for 200 actuations. Each actuation of PROVENTIL® HFA delivers 108 µg of albuterol sulfate from the mouthpiece, equivalent to 90 µg of albuterol base, and the canister is rated for 200 actuations.

Four samples of the MicroChamber® device were tested, with each of the two different MDI medications. A total of 8 sample spacers were thus tested. A single MDI of each drug was used for all four sample spacer devices for consistency. Separate measures of drug delivery from the MDI alone, without spacer attachment, were made for comparison and dose verification.

Particle size measures were performed using an Anderson 8 stage Cascade Impactor with a USP induction throat. Separate measures of the drug delivery from the MDI alone, without attachment to a reservoir, were made for comparison of particle size distribution. A flowrate of 28.3 Lpm (±0.5 L) was maintained through the impactor, and verified using a Fischer & Porter flowrater, calibrated with NIST certification, at the inlet of the impactor, with

Figure 2. Total & Respirable Dose of Albuterol (CFC) and albuterol sulfate (HFA)*
*120 mcg albuterol sulfate equivalent to 100 mcg albuterol base



Micro - MicroChamber; CFC- CFC formulated albuterol;
HFA - HFA formulated albuterol sulfate

all plates and final filter in place. The respirable dose fraction is reported as the cumulative dose (or percentage of total dose) below 4.7 µm.

Ten actuations were wasted from an MDI prior to testing. For particle size measures, a total of five separate MDI actuations were discharged. MDI's and reservoir devices were attached to the USP throat, flush and vertical with the face of the throat inlet. The impactor pump was turned on prior to MDI discharge. Each MDI actuation was followed by a 30 second pause, with shaking between actuations. The impactor pump was kept running until approximately 20 seconds after the last MDI actuation. A log of MDI discharges was kept, and no MDI was used beyond 50% of its rated capacity of 200 actuations.

Figure 3. PARTICLE SIZE DISTRIBUTIONS
MicroChamber (n=4) vs MDI Alone
CFC-albuterol formulation

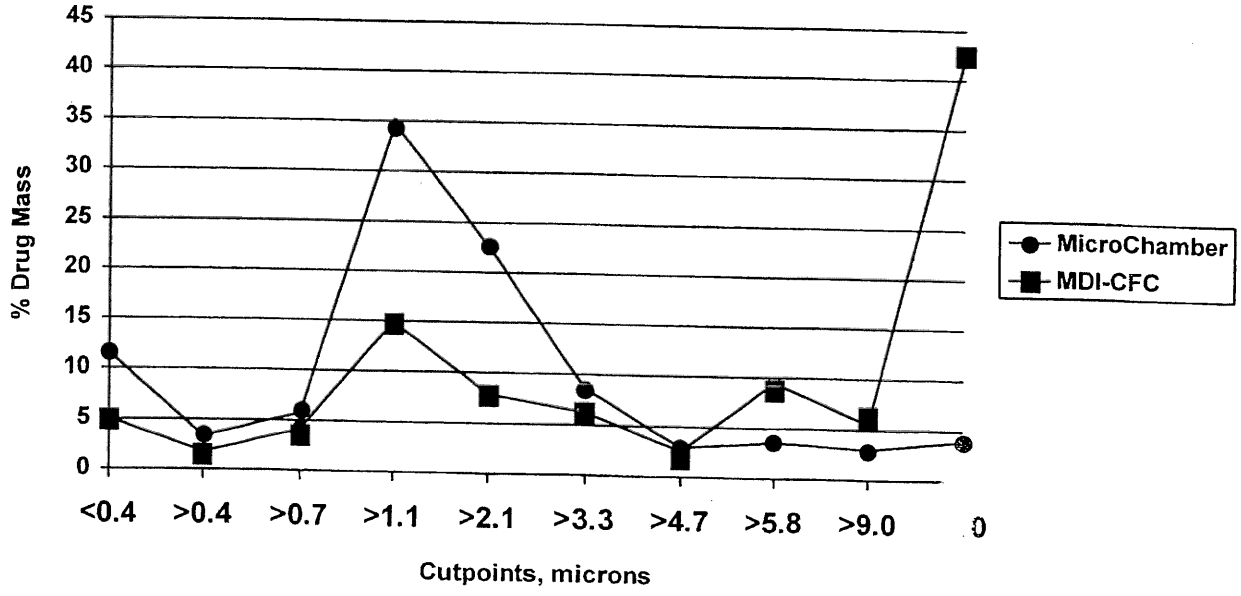
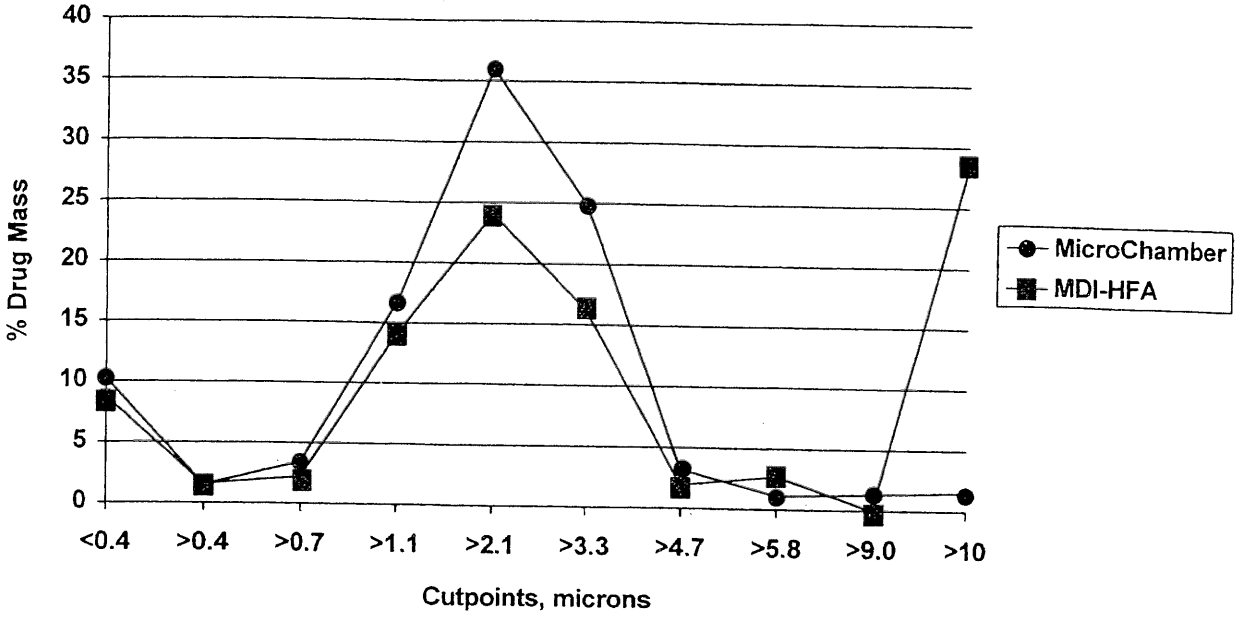


Figure 4. PARTICLE SIZE DISTRIBUTIONS

MicroChamber (n=4) vs MDI Alone

HFA-albuterol formulation*

***120 mcg HFA albuterol sulfate = 100 mcg CFC albuterol base**



Drug from the impactor stages was washed using a 0.1 N HCl solvent, and the resulting solution analyzed using a Beckman DU 640 spectrophotometer, at 276 nm. A standard curve was obtained from serial dilutions of a measured concentration for each drug with a least squares regression line fitted to the data points. Linear regression was used to predict drug mass from the measured absorbance of the samples.

Results:

Figure 2 gives the total and respirable dose measured by cascade impaction for the two drugs tested with the MicroChamber®.

Doses reported for the MicroChamber® represent means and standard deviations for the four samples tested. Measurement of the MDI alone with albuterol-CFC (MDI-CFC) shows that approximately 40% of the 91 µg dose is in the respirable size fraction. Use of the MicroChamber® (Micro CFC) reduced the total dose, but increased the respirable fraction to approximately 86%, or 61 µg, of the available dose.

PROVENTIL® HFA delivers albuterol sulfate, with 120 µg of albuterol sulfate equivalent to 100 µg of albuterol base in the CFC formulation. The sulfate was measured in the assay, and is reported here (Figure 2). The MDI of albuterol-HFA (MDI-HFA) alone has a higher respirable fraction of approximately 67% of total dose, compared to 40% with albuterol-CFC. Use of the MicroChamber® (Micro HFA) reduced the total dose from the MDI, but increased the respirable dose to 98.8 µg, or 93% of available dose. This is equivalent to 82 µg of albuterol base in the CFC formulation, which is higher than the 61 µg obtained with albuterol-CFC.

The effect of the MicroChamber® reservoir on particle size distribution with the CFC formulation of albuterol is shown in Figure 3. The MDI with no reservoir shows a typical peak of drug particles larger than 10 µm. This is due to inertial impaction of high-velocity, large particles in the sizing instrument, when using the MDI with no reservoir device.

In contrast, use of the MicroChamber® reservoir device reduces particle size loss in the large, >10 µm range, typically lost in the throat of either the patient or the impactor sizing instrument. There is a greater proportion of drug in the "respirable" size range of < 4.7 µm.

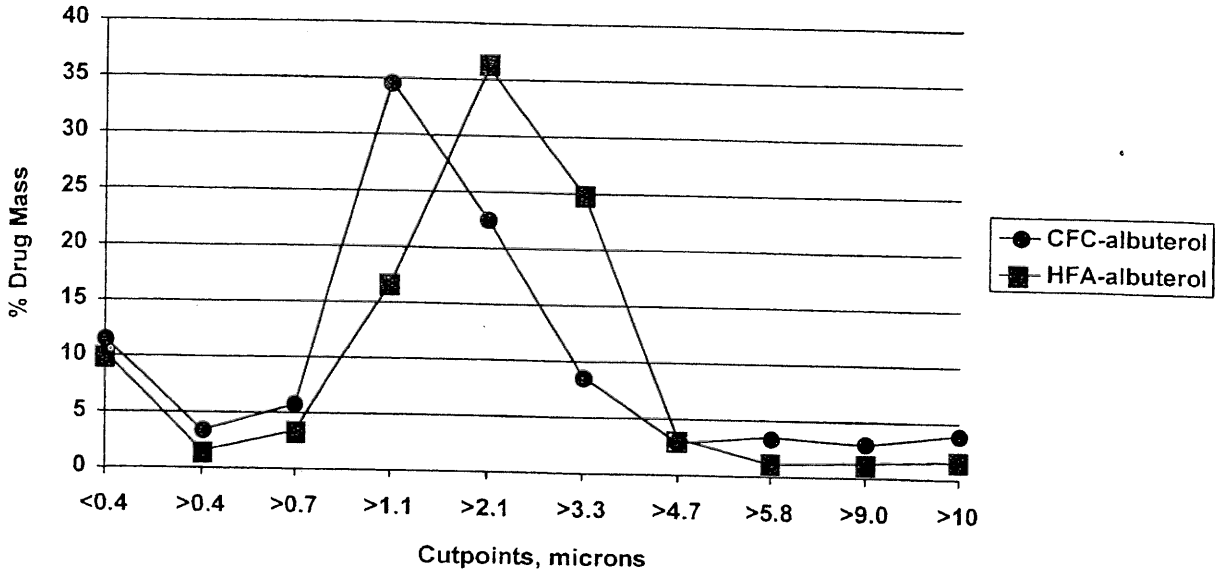
Figure 4 illustrates the same effect of the MicroChamber® on particle size distribution with the HFA-albuterol. Again, throat loss is replaced with more drug in the 1 to 4.7 µm size range. There is also a greater proportion of drug in the < 4.7 µm range with the HFA-albuterol MDI compared to the CFC-albuterol MDI in Figure 3.

A direct comparison of particle size distributions using the MicroChamber® with either the CFC or the HFA formulation of albuterol is shown in Figure 5. There was a shift of the size distribution to slightly larger particles with the HFA formulation compared to the CFC formulation, in the < 4.7 µm size range. This data indicates the HFA formulation can offer more drug amount in the respirable range, since drug mass increases exponentially with particle size diameter.

Figure 5. PARTICLE SIZE DISTRIBUTIONS

MicroChamber (n=4) with CFC- vs HFA-albuterol*

***120 mcg HFA albuterol sulfate = 100 mcg CFC albuterol base**



Clinical Application:

Because the MicroChamber® is a true spacer with no oneway inspiratory valve, and not a holding chamber, patient education and correct use is essential to obtain dose results equivalent to those measured in the study. The user must be educated to:

- Begin inspiration simultaneously with actuation of the MDI.
- Inhalation ***after*** MDI actuation may decrease lung dose and increase oropharyngeal impaction, since there is no inspiratory valve to contain the plume.
- Exhaling ***against*** the actuation will result in loss of dose.
- Maintain an inspiratory flowrate of approximately 30 Lpm.

The results obtained indicate that the MicroChamber® spacer can improve the respirable fraction available to the patient, with both PROVENTIL® and with PROVENTIL® HFA, compared to use of an MDI alone. Use of the HFA formulation of albuterol appears to result in a higher dose fraction available to the patient, with either an MDI alone, or with an attached reservoir device such as the MicroChamber®. Total and respirable doses measured are equivalent to those obtained with holding chambers such as the AeroChamber® or the Aerosol Cloud Enhancer (ACE®) when tested with albuterol.

MicroChamber® is a registered Trademark of RDS, Inc.

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