Characterization of Particle Size Distributions and Respiratory Tract Deposition of Albuterol Sulfate Metered Dose Inhalers

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INTRODUCTION

- Metered dose inhalers (MDIs) are commonly used to deliver therapeutic agents to the lung.
- The amount of inhaled drugs deposited on lung airways is important to quantify to assist with in vitro/in vivo extrapolation.
- Lung dose depends on many factors such as the formulation, excipients, breathing maneuvers, and thermodynamic processes such as propellant evaporation and spray atomization that affect deposition in the mouth-throat.

The objective of this study was to estimate lung deposition of aerosols delivered from albuterol sulfate MDIs. In support of this objective, droplet sizes emitted from MDIs and downstream of mouth-throat models were measured using in vitro techniques.

MATHEMATICAL MODEL

A multiple-path particle dosimetry (MPPD) model was previously developed based on airway morphometry measurements of human lung geometry and ventilation distribution [1]. The model calculates lung deposition by airway generation, lobe, or region based on the deposition mechanisms of inertial impaction, sedimentation, and diffusion. Breathing parameters such as tidal volume and frequency are input into the model. Oropharyngeal (OP) deposition estimates are based on upper respiratory tract deposition in human volunteers [2].

For this study, the MPPD model was run for two cases:

1. Estimate oropharyngeal and lung deposition using droplet sizes emitted from MDIs
2. Estimate lung deposition using particle sizes from cascade impactor experiments

METHODS AND EQUIPMENT

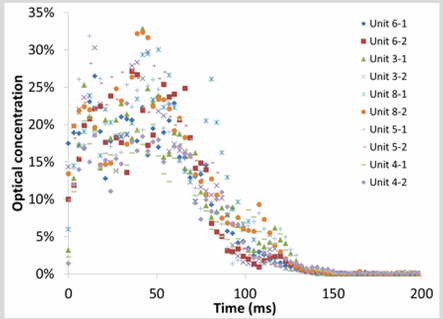
LASER DIFFRACTION:

- Volumetric particle size distributions (PSDs) were measured from each of the same five MDIs using static laser-light diffraction (Sympatec HELOS).
- Measurements were made at 3 ms intervals at a distance of 2 cm from the laser beam for a period of 200 ms.
- Two measurements were made from each MDI and the results were averaged.

CASCADE IMPACTION:

- Aerodynamic PSDs were determined using a Next Generation Impactor (NGI) at a flow rate of 30 L/min.
- A USP throat or Alberta Idealized Throat (AIT, Copley) was employed.
- For each of the same five MDIs, one NGI experiment was performed using each throat model.
- Each NGI experiment consisted of two actuations and collected samples were assayed by LC-MSD.

FIGURE 1



Optical concentration data from the laser diffraction measurements for the five MDIs.

RESULTS & DISCUSSION

LASER DIFFRACTION:

The average volume mean diameter (VMD) emitted from the MDIs was 6.84 ± 0.16 µm with a GSD of 2.10 ± 0.07. Optical concentration data suggested that nearly all of the mass was expelled from the actuator within 150 ms (Figure 1).

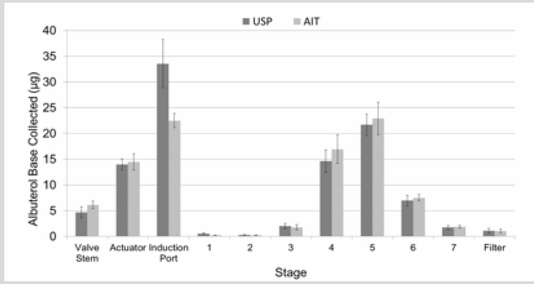
CASCADE IMPACTION:

For NGI experiments, the MMAD and GSD using the USP throat were 1.97 ± 0.10 µm and 1.55 ± 0.05. Using the AIT, the MMAD and GSD were 1.97 ± 0.06 µm and 1.55 ± 0.04. Both physical throat models resulted in significant removal of larger droplet sizes (Figure 2). Higher deposition was observed in the USP throat model (40.7%) than in the AIT model (30.0%).

MODELING RESULTS:

Respiratory tract deposition was calculated using a tidal volume of 500 mL and an inhalation time of 1 sec. Estimated OP deposition was 46% for the PSDs emitted from the MDIs. Lung deposition fractions for the PSDs emitted from the MDIs and from the NGI experiments were 23 and 24%, respectively, and were consistent with previous experimental studies on HFA MDI deposition in airway replicas [3]. Lung airway deposition profiles were similar for the two cases, with slight differences in deposition magnitude that can be attributed to differences in OP deposition (Figure 3).

FIGURE 2

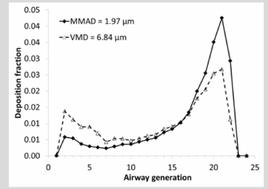


Comparison of the amount of albuterol base collected per actuation for the USP throat and the AIT models.

CONCLUSIONS

An accurate quantification of particle sizes and respiratory tract deposition efficiencies is essential for evaluating the efficiency of drug delivery devices. Validated lung deposition models provide an important link in the drug delivery/therapeutic response continuum.

FIGURE 3



Lung airway deposition estimates using PSDs emitted from MDIs as determined by laser diffraction and by NGI experiments.

TABLE 1

Size (µm)	GSD	Deposition Fraction OP	TB	PU	Lung
VMD = 6.84 (via laser)	2.10	0.46	0.13	0.10	0.23
MMAD = 1.97 (via NGI using USP or AIT throat models)	1.55	n/a	0.09	0.15	0.24

Deposition results from the MPPD model.

ACKNOWLEDGMENTS

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