Modifications to the Multiple-Path Particle Dosimetry Model for Improved Predictions of Lung Deposition from Metered Dose Inhalers

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INTRODUCTION

• The Multiple-Path Particle Dosimetry (MPPD) model has been widely used to calculate lung deposition of inhaled particles [1].

• The MPPD software was originally designed for inhalation of environmental aerosols.

• The calculation of lung dose from drug delivery devices such as metered dose inhalers (MDIs) presents additional challenges:

- droplets emitted from MDIs enter the mouth-throat region at high velocities, leading to enhanced deposition

- the breathing maneuver during an MDI spray is much different than a normal inhalation

- In this study, modifications were made to the MPPD software to address the above limitations for its use in estimating lung dose from MDIs. Modifications include:

  - improved mouth/throat deposition estimates using in vitro data

  - bolus delivery model

- To support this effort, in vitro experiments were conducted to measure particle size distributions (PSDs) and to estimate mouth-throat deposition from MDI formulations using various drug and co-solvent concentrations and primary drug particle sizes.

APPROACH

In Vitro Experiments

- Particle size data were obtained for albuterol sulfate (AS) and beclomethasone dipropionate (BDP) model systems with varying ethanol and oleic acid concentrations and active drug particle sizes.
- Primary particle sizes were measured using static laser-light diffraction.
- Aerodynamic particle sizes were measured using cascade impaction.
- An Alberta Idealized Throat or a USP throat was used to estimate deposition in the mouth/throat region.

Modeling

• Two modifications were made to the MPPD model to improve predictions of lung deposition from MDIs:

- improved mouth/throat deposition estimates using results from the in vitro experiments

- new bolus delivery model to account for particle inhalation from an MDI

- A computational fluid dynamics (CFD) model of the mouth/throat region was used to estimate particle deposition sprayed from MDIs

METHODS

In Vitro Experiments

Laser Diffraction:

• Volumetric PSDs were measured for each MDI formulation 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.

Cascade Impaction:

• Aerodynamic PSDs were determined using a Next Generation Impactor (NGI) at a flow rate of 30 L/min.

• An Alberta Idealized Throat (AIT, Copley; coated with glycerol) or USP Throat was used for the induction port.

• Three cans were tested from each MDI batch. Each NGI experiment consisted of two actuations, and collected samples were assayed by LC-MS.

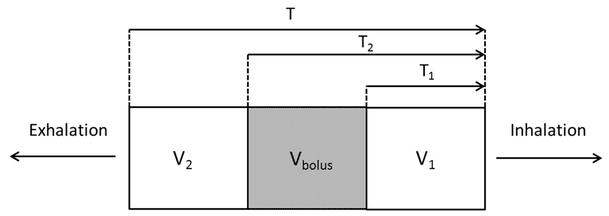

Figure 1: Schematic representation of the inhaled bolus model. Inhaled tidal air is represented by clean air volumes V_1 and V_2 and bolus volume V_{bolus}. The time points for bolus injection (T_1 and T_2) must be input into the MPPD model.

Modeling

MPPD Model:

• The semi-empirical curve for oropharyngeal deposition originally included in the MPPD model was derived from human studies of particle deposition under natural breathing conditions [2].

• A new semi-empirical curve for mouth/throat deposition was developed based on deposition measurements in the AIT and USP induction ports.

• The MPPD model originally assumed that the inhaled particle concentration was constant during the entire breathing cycle.

• A new bolus delivery model was implemented to account for the inhalation of particle-free clean air before and after the bolus (Fig. 1).

CFD Model:

• The VCU mouth/throat geometry [3] was used to simulate inhaled airflow, particle deposition, and sprayed particles (Fig. 2).

• The k-ω SST turbulence model was used for transitional to turbulent airflow simulations at 15-60 L/min.

• Particles were naturally released from the oral inlet for model validation.

• Dry solid particles were released in a “solid-cone” spray formation from the oral inlet center to simulate an MDI spray.

RESULTS

Mouth/Throat Deposition

- Volume median diameters (VMDs) ranged from 3.03-9.43 µm and from 4.11-5.36 µm for the AS and BDP model systems, respectively.
- The amount deposited in induction ports ranged from 24-69% and showed a general increasing trend with VMD (Fig. 3).
- A linear trend line was fit to the induction port data to estimate mouth-throat deposition in the MPPD model.

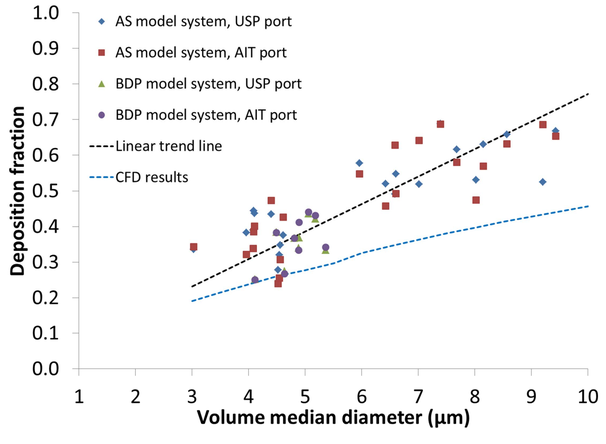

Figure 3: Deposition fractions in the USP and AIT induction ports for the AS and BDP model systems. A best-fit linear trend line and the results from the CFD spray modeling are also shown.

Lung Deposition

- Average MMADs ranged from 1.80-5.72 µm and from 0.73-2.61 µm for the AS and BDP model systems, respectively.
- MPPD predictions using the bolus delivery model showed a significant impact of bolus times on lung deposition (Table 1).
- Lung deposition predictions were obtained using the MMADs for the AS and BDP model systems. A breathing maneuver with a tidal volume of 5000 mL, 3 sec inhalation time, bolus injection time of 0.6 seconds starting 0.4 seconds after the start of the breath were used.
- AS model system:
  TB: 4.2-32.9%, PU: 5.0-35.6%, Total: 20.7-52.4%
- BDP model system:
  TB: 4.0-11.7%, PU: 14.3-31.5%, Total: 18.2-43.2%

Table 1: Lung deposition predictions using bolus delivery compared with the non-bolus (constant) inhalation. MMAD = 2.5 µm, GSD=1.8.

Bolus interval (sec)	Lung deposition (%)		
	TB	PU	Lung
Non-bolus	12.9	19.3	32.1
0 – 0.25	16.0	49.0	65.0
0.25 – 0.5	17.4	35.8	53.2
0.5 – 0.75	19.1	9.5	28.6
0.75 – 1.0	4.8	0	4.8

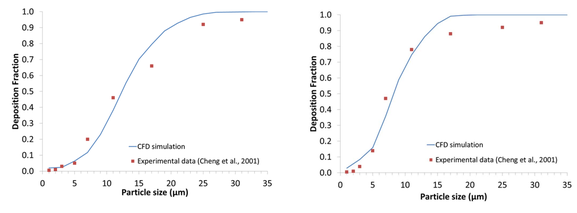

Figure 4: Comparison of CFD predictions of naturally released particle deposition in the VCU model with experimental data.

RESULTS

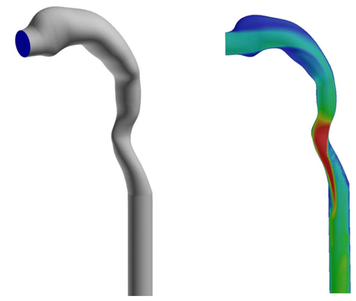

Figure 2: Left: Angular view of the VCU idealized mouth/throat geometry. Right: Airflow velocity contours along a centerline of the model.

DISCUSSION

• Improved oropharyngeal deposition estimates and the bolus delivery model had significant impacts on lung deposition predictions from MDIs.

• A wide range of MMADs were reported for both AS and BDP model systems, resulting in widely varying lung deposition predictions.

• CFD deposition predictions compared well with experimental data for naturally released particles, but spray deposition results in the mouth-throat geometry under-predicted the induction port deposition data (Fig. 3).

• Future work will focus on improving CFD predictions of spray deposition by accounting for more realistic spray atomization and droplet composition.

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www.rddonline.com/resources/tools/models.php.