In Silico OIDP Development

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Introduction

- **In Silico** assessment of orally inhaled products:
  - Includes the use of physically realistic computational fluid dynamics (CFD) simulations that can capture aerosol formation, inhaler-patient interface, airway deposition & PK
  - Aerosol formation
    - Powder fluidization and deaggregation
    - Spray formation
  - Inhaler-patient interface
    - Aerosol deaggregation and size change
    - Device and mouth-throat deposition
  - Lung deposition and subsequent absorption
    - Regional and local deposition
    - Dissolution (~concentration and solubility)
    - Absorption (~concentration and partitioning)

Concurrent CFD and in vitro analysis
Outline

- What is CFD modeling
- Why is concurrent analysis important
- Examples of CFD inhaler analysis and optimization
- CFD assessment of regional and local lung dose
- Use of CFD to compare MDI and DPI lung delivery
- Model validations with *in vivo* data
- Discussion of implementation
What is CFD Modeling?

- Transport equations are solved in realistic 3D geometries
  - Geometries are constructed from medical scans and literature data
  - CFD process subdivides geometry into small discrete volumes
  - These control volumes make up the grid or mesh

- As with experiments, “best practices” should be followed
  - Use of hexahedral (brick) control volumes
  - Testing of mesh independence
  - Validation with experimental results
Concurrent *In Vitro*–CFD Analysis

- Testing using both *in vitro* experiments and CFD simulations
- Concurrent analysis seeks to leverage the strengths of each method
  - *In vitro* testing
    - Provide initial size distribution of the aerosol
    - Benchmark deposition within a realistic airway model
    - Used to initially validate CFD results
  - CFD Modeling
    - Analyze experimentally difficult systems (entire TB or alveolar airways) and provide additional resolution of deposition
    - Allows modification and optimization of device performance
CFD Inhaler Analysis and Optimization
# CFD Inhaler Analysis

Examples of quantitative inhaler analysis and design using CFD

<table>
<thead>
<tr>
<th>Inhaler type</th>
<th>Design variable</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPI with spray-dried mannitol</td>
<td>Powder dispersion vs. Integral scale strain rate</td>
<td>Coates et al. (2006) <em>J. Pharm. Sci.</em> 95(6) 1382-1392</td>
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<tr>
<td>DPI with carrier-based formulations</td>
<td>Powder dispersion vs. Impaction velocity and capsule airflow</td>
<td>Shur et al. (2012) <em>AAPS J.</em> 14(4) 667-676</td>
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<td>Spray inhaler with aqueous solution</td>
<td>Device deposition vs. turbulence intensity</td>
<td>Hindle and Longest (2013) <em>JAMPDD</em> 26(5) 237-247</td>
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CFD Assessment of Regional and Local Lung Dose
Conducting Airway Deposition

- To address the complexity of the tracheobronchial airways, a stochastic CFD model approach was developed
  - Build stochastic individual paths (SIPs) into each lobe
- Incorporated realistic inhalation flow profiles which are known to influence aerosol drug delivery
A 3D space filling alveolar model is being used at VCU to predict alveolar deposition

- Model extends from terminal bronchioles for 5 generations
- Simulations with more alveolar generations produced identical results
- Evaluated quick and deep and slow and deep inhalation
Alveolar Model Deposition

- Alveolar deposition efficiencies for quick and deep (QD) inhalation and breath-hold (BD)
  - Predictions are largely different from currently used straight tube analytical expressions

![Quick and Deep Inhalation](image1)

![Breath Hold](image2)

\[ X (\text{µm s}) = d^{1.4} \text{particle}^{0.73} \]

\[ X (\text{µm s}) = d^{3.03} \text{particle}^{1.48} \]
Initial Conditions for Dissolution

- **Microdosimetry factor** for light activity conditions ($Q_T = 25$ L/min)

- **Microdosimetry factor** represents the local concentration vs. the area-averaged for the bifurcation

<table>
<thead>
<tr>
<th>Model</th>
<th>Color Map</th>
<th>$\chi_{\text{max}}$ (cm$^{-2}$)</th>
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<tbody>
<tr>
<td>$A_n$</td>
<td>[Image]</td>
<td>3.96 (cm$^{-2}$)</td>
</tr>
<tr>
<td>$A_c$</td>
<td>[Image]</td>
<td>28.1 (cm$^{-2}$)</td>
</tr>
<tr>
<td>$B_n$</td>
<td>[Image]</td>
<td>90.5 (cm$^{-2}$)</td>
</tr>
<tr>
<td>$B_c$</td>
<td>[Image]</td>
<td>323.4 (cm$^{-2}$)</td>
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Case Study: Use of CFD to Compare MDI and DPI Lung Delivery
MDI vs. DPI Lung Delivery

- Comparison of MT-TB delivery from an MDI and DPI using “correct” and “incorrect” inhalation profiles

(a) MDI and MT-TB model
MDI with mouthpiece

(b) DPI and MT-TB model
DPI mouthpiece
MDI vs. DPI Lung Delivery

MDI Delivery (Flovent HFA)
- Turbulent and compressible flow
- Time dependent
- Multiple species with rapid evaporation
- Large aerosol size change

DPI Delivery (Flovent Diskus)
- Turbulence and high speed jets
- Time dependent
- Fluidization and deaggregation of the powder
- Highly polydisperse aerosols
Inhalation Flow Profiles

“Correct” and “incorrect” inhalation profiles for the MDI and DPI

<table>
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<tr>
<th>Combination</th>
<th>Waveform</th>
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<tbody>
<tr>
<td>Correct MDI</td>
<td>SD</td>
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<tr>
<td>Correct DPI</td>
<td>QD</td>
</tr>
<tr>
<td>Incorrect MDI</td>
<td>QD</td>
</tr>
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<td>Incorrect DPI</td>
<td>SD</td>
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MDI vs. DPI Lung Delivery

- Comparison of *in vitro* results of drug mass deposition with CFD model predictions for the DPI
MDI vs. DPI Lung Delivery

- Comparison of *in vitro* results of drug deposition with CFD model predictions for the MDI
  - First study to report good agreement between CFD predictions and deposition results in a MT-TB model with an MDI
MDI vs. DPI Lung Delivery

- MT and upper TB deposition with “correct” (top row) and “incorrect” (bottom row) inhalation profiles
- With “correct” inhalation, MDI delivers 2x dose to the upper TB with ½ the loss in the MT
- With “incorrect” inhalation, MDI still performs better than the DPI

Longest et al. (2012) Pharm. Res. 29: 1670-1688
MDI vs. DPI Lung Delivery

- Regional deposition fraction of drug mass with the MDI and DPI
  - MDI delivers 2x drug to Trachea-B3 (correct usage)
  - DPI delivers 2x drug to B4-B7 (correct usage)
  - Total TB deposition is nearly identical between MDI and DPI with correct inhalation
  - With incorrect inhalation, DPI TB dose decreases by 2x
Case Study: *In Vivo* Validations
**In Vivo Validations**

- Novolizer DPI operated with a PIFR of 99 LPM
  - *In vivo* scintigraphy from Newman et al. (2000)
  - CFD SIP model analysis with alveolar predictions

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<th>In Vivo Results from 2D Gamma Scintigraphy</th>
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<tr>
<td>Mouth-throat (with mouthpiece)</td>
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<td>Central lung (20% area)</td>
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<td>Peripheral lung (80% area)</td>
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<th>CFD Predictions using SIP and Alveolar Models</th>
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<tbody>
<tr>
<td>Mouth-throat (with mouthpiece)</td>
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<td>Central lung (B1-B7)</td>
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<tr>
<td>Peripheral lung (B8-B24)</td>
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Discussion of \textit{In Silico} Implementation
**In Silico Implementation**

- **Research**
  - Inhaler design: Well accepted
  - Lung deposition: Models in development (SIP approach)

- **Bioequivalence testing**
  - Current collaboration between VCU / Univ. of Florida / Bath
    - CFD model development and validation with *in vitro* data
    - *In vivo* PK data for multiple powder formulations
    - Comparison of local CFD deposition results and PK data

- **FDA submissions**
  - What components of model predictions are useful?
  - What model validation aspects are needed?
    - *In vitro* vs. *In vivo* comparisons
    - Benchmarking datasets
## Acknowledgements

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<th>VCU Faculty</th>
<th>Dr. Michael Hindle and Dr. Peter Byron of the VCU Department of Pharmaceutics</th>
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<tr>
<td><strong>US FDA</strong></td>
<td>Dr. Sau Lee and Dr. Renish Delvadia</td>
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