Dry Powder Inhaler Performance: A CFD-Euler/Lagrange Study

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Content of the Lecture

- Introduction to inhaler operation and performance
- CFD – Euler/Lagrange methods for inhaler applications
- E/L computation of Carrier Particle motion and statistics
- Micro-scale simulations of the flow about a cluster based on LBM
  - Detachment probabilities of drug particles by fluid stresses
- Lagrangian tracking with wall-collision detachment model
- Lagrangian tracking of fine particles and deposition
- Conclusions / Outlook / Collaborations
Nowadays many drugs as powder formulation are administered through inhalation.

- The size of the particles needs to be smaller than about 5 μm in order to ensure that they are transported up to the alveoli of the lung.
- Such fine powders are very cohesive and extremely difficult to be dispersed in an inhaler by the airstream during the inhalation period.
- Two different drug formulations are commonly used, which have to be re-dispersed in the breathing flow through the inhaler.

**Blending of larger carrier particles (about 50-100 μm) with fine agent particles**

**Agglomerated drug powder (particles about 1-5 μm), see Finlay (2001)**

- Flow stresses and wall impacts

> The flow structure in the inhaler must insure aerosolisation (dispersion) of the fine drug powder
Unfortunately, although hundreds of different inhaler types are on the market, their efficiency (emitted over loaded fine particle fraction) is only between 20% and 40%

This calls for optimisation !!!!

The different flow structures have to induce particles motion and drug aerosolisation
Computational fluid dynamics (CFD) is a promising tool for inhaler analysis, design and optimisation. Numerous studies were performed already, see Sommerfeld et al. (2019). The Euler/Lagrange approach is most suitable for such application!!!

- Tracking of: fine particles (deposition) coarse particles (wall collisions)

The very complex flow structure inside the inhaler (highly swirling flow) requires more sophisticated turbulence models (LES, RANS with k-ω-SST model).

- Particles are not individual particles however, agglomerates (1000nds of fine particles) or clusters consisting of carrier (≈ 100 μm) and 1000nds attached drug particles (< 5 μm).
Lagrangian Particle Methods (Point-Particles)

- **DPM with hard-sphere collisions**
  - Particles are treated as point-masses
  - Particle motion driven by fluid-dynamic (drag and lift) and external forces
  - Only binary collision of two particles at a time (time step: event driven)
    - Deterministic inter-particle collisions
    - Stochastic inter-particle collision model

- **Discrete element methods (DEM)**
  - Individual particles are treated as point-masses
  - Particle motion caused by fluid-dynamic, external and contact forces (Van der Waals, electrostatic, ..)
  - Multiple particle contacts (finite sized particles)
  - Contact model: spring, dashpot, friction slider
  - *Limited by the number of possible particles*

- Clusters or agglomerates are considered as a single entity (one point particle)
- Additional models are required for:
  - Extended resistance coefficients
  - Flow detachment of drugs
  - Carrier-wall collision and detachment
  - Re-deposition of drug particles

- Particles within agglomerates are tracked independently considering interactions (adhesion)
- Fluid forces accounting for particle interactions are needed (lift ?? swarm effects ???)
- In this way a cluster cannot be tracked properly !!!
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RANS Calculations of Inhaler; Carrier Particle Behaviour

- Simulation of a stationary flow through the inhaler using OpenFOAM

- RANS calculations with k-ω-SST turbulence model using a tetrahedral mesh (steady-state)
- Flow rates between 30 and 100 l/min
- Tracking of 1,024 carrier particles accounting for all forces (Sommerfeld et al. 2008; Crowe et al. 2012)
  - drag force
  - gravity/buoyancy
  - added mass / pressure
  - slip/shear lift
  - slip/rotation lift !!!
  - torque on the particle

- The maximum total tracking time 3 sec
- Dynamic Lagrangian time step $\Delta t_L = 0.2 \times \min(\tau_p, T_L)$
- Turbulent dispersion model: single-step Langevin model
- Wall collisions: Impulse equation with Coulombs law of friction: $e = 0.9$; $\mu = 0.1$ (standard)

1.4 million grids

Carrier particle sizes: mono-sized, 50 μm, 100 μm, 200 μm
## Carrier Particle Behaviour

### Fluid Velocity

<table>
<thead>
<tr>
<th>Flow Rate</th>
<th>Grid Cells</th>
<th>Inlet Velocity</th>
<th>Outlet Velocity</th>
<th>Velocity Near Grid</th>
<th>Velocity Reservoir</th>
<th>Swirl Chamber</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 l/min</td>
<td>300,000</td>
<td>25.0 m/s</td>
<td>13.5 m/s</td>
<td>70 m/s</td>
<td>48 m/s</td>
<td>43 m/s</td>
</tr>
<tr>
<td>100 l/min</td>
<td>400,000</td>
<td>36.0 m/s</td>
<td>19.3 m/s</td>
<td>80 m/s</td>
<td>75 m/s</td>
<td>64 m/s</td>
</tr>
</tbody>
</table>

### Turbulent Kinetic Energy

- 110 μm
- $T_r = 0.04$ s
- $N_{wc} = 100$
Highly swirling flows are never stable. 

- Iter = 2000
- Iter = 4000
- Iter = 6000
- Iter = 8000

vortex precession
Carrier Particle Behaviour 4

- Initial carrier particle lifting for a flow rate of 60 l/min and a size of 100 μm.

Time = 1 ms  Time = 3 ms  Time = 4 ms  Time = 5 ms

Time = 6 ms  Time = 7 ms  Time = 9 ms  Time = 10 ms
Carrier Particle Behaviour 5

- Particle-phase statistics along all trajectories through the inhaler (flow interaction)

- Transverse lift forces are very important
- Extremely high relative velocities yielding large $Re_p$

110 $\mu$m

50 $\mu$m: $N_{wc} = 67$
110 $\mu$m: $N_{wc} = 100$
500 $\mu$m: $N_{wc} = 300$
Wall collision statistics for different carrier particle sizes and flow rates:

- The wall collision number per particle reduces with particle size and flow rate.

Wall collisions induce extreme high angular velocities

- Magnus lift force !!!
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Lattice-Boltzmann-Method (LBM) simulation of fluid dynamic forces on drug particles and estimation of flow detachment probability (coverage degree 50 \%, D_{\text{fine}}/D_{\text{carrier}} = 5/100, n_{\text{fine}} = 882).

Glass bead carrier treated with tungsten carbide particles in a ball mill (TU Graz):

→ $F_{\text{vdw}} = 47.90 \pm 30.91 \text{ nN}$
→ Lift-off is not likely to occur
LBM / Drug Detachment by Fluid Stresses 2

- Statistical sliding and rolling fraction of drug particles as a function of Reynolds number ($D_{\text{drug}}/D_{\text{carrier}} = 2.45/100$, coverage = 25%, SS17 / TC 8h, measured van der Waals (University Graz): 47.90 ± 30.91 nN)

\[ F_t > \mu (F_{vdW} - F_n) \]

\[ M_{hyd} + F_t R_d + F_n a > F_{vdW} a \]
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RANS calculations with k-ω-SST turbulence model OpenFOAM®
- Particle tracking in the beforehand obtained quasi-steady flow field starting in the capsule reservoir
- Tacking time step = 1 μs
- Flow rate: Cyclohaler (90 l/min); Unihaler (60 l/min);
- Only one-way coupling is considered
- Forces: drag, gravity, slip-shear lift, slip-rotation lift, added mass and pressure gradient (Crowe et al. 2012, Sommerfeld and Schmalfuß 2016)
- Dispersion: single-step Langevin model (parameters from k-ω model)
- For each cluster-wall collision the drug detachment (only lift-off) due to inertia > van der Waals is determined (Cui & Sommerfeld 2019):
  - Adhesion parameters (drug/carrier, TC 8h)
  - Elastic collision, carrier-wall friction (μ_W)
  - Impact velocity; impact angle
  - PDF of drug size and PDF adhesion force
- After a cluster wall collision, the drug particles are again homogeneously distributed in the carrier surface
- Finally the total detachment is obtained by counting all detached drugs
Two inhaler geometries are considered: Cyclohaler® & Unihaler (University Kiel)

Cyclohaler® (90 L/min)
- 411,869 tetrahedral cells

Unihaler (60 L/min)
- 1,444,712 tetrahedral cells
Wall Collision Detachment 1

- Pressure drop and streamlines of the simulated stationary flow through the inhaler:

**Cyclohaler® (90 L/min)**

**Unihaler (60 L/min)**
- Setting: Tracking Time = 1.0 s, Carrier/Drug Size = 104.9/2.45, Coverage = 25%, $\mu_w = 0.1$, Perfect Elastic, Pressure Drop = 4 kPa, Surface Treatment SS17/TC 8h.

<table>
<thead>
<tr>
<th></th>
<th>Unihaler (99.9 %)</th>
<th>Cyclohaler (98.9 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC/Particle</td>
<td>212 ± 320</td>
<td>55 ± 51</td>
</tr>
<tr>
<td>Particle Residence Time</td>
<td>0.10 ± 0.09 s</td>
<td>0.06 ± 0.06 s</td>
</tr>
</tbody>
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The same flow field was considered for analysing fine particle deposition ($0.5 \, \mu m < d_p < 5 \, \mu m$) within the two inhaler types:

**Deposition of fine particles was based on an energy balance:**

\[
E_{k1} \leq \Delta E_{vdw} + E_d \\
\Delta E_{vdw} = - \int_{z_0}^{\infty} \frac{H}{6 \pi z^3} \pi a^2 \, dz \\
k^2 = \frac{E_{k1} - E_d}{E_{k1}} \\
U_{crit} = \left(1 - k^2 \right)^{1/2} \cdot \frac{H}{\pi d_{p1} z_0^2 \sqrt{6 \rho_p \rho_c}}
\]

Deposition if: \[ \bar{U}_{wall} \cos \varphi \leq U_{crit} \]

<table>
<thead>
<tr>
<th>H</th>
<th>5 \cdot 10^{-19} \text{ J}</th>
</tr>
</thead>
<tbody>
<tr>
<td>k</td>
<td>0.5 / 0.7</td>
</tr>
<tr>
<td>$z_0$</td>
<td>40 A</td>
</tr>
<tr>
<td>$p_c$</td>
<td>5 \cdot 10^9 \text{ Pa}</td>
</tr>
</tbody>
</table>
Deposition model based on a simplified JKR theory according to Beach & Dunn (1992) which was also applied by Milenkovic et al. (2013):

Critical impact velocity based on the work of adhesion and the maximum contact area:

\[
U_{\text{crit}}^2 \sim - \frac{2 W_A}{m_P} = \frac{8 a_m^2 F_A}{3 d_P}
\]

\[
U_{\text{crit}} = \left( \frac{2 E}{d_P} \right)^{10/7}
\]

Effective stiffness parameter

\[
E = 0.51 \left[ \frac{5}{4} \frac{\pi^2}{Q_p^{2/3}} (k_p + k_s) \right]^{2/5}
\]

\[
k_P = \frac{1 - \nu_P^2}{\pi E_P}
\]

\[
k_s = \frac{1 - \nu_S^2}{\pi E_S}
\]

Deposition if: \( \bar{U}_{\text{wall}} \cos \varphi \leq U_{\text{crit}} \)

<table>
<thead>
<tr>
<th></th>
<th>Polystrene</th>
<th>Lactose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poisson ratio</td>
<td>0.4</td>
<td>0.35</td>
</tr>
<tr>
<td>Young’s modulus</td>
<td>1.0 GPa</td>
<td>4.1 GPa</td>
</tr>
</tbody>
</table>

Initial position of 2541 particles
Particle sizes between 0.1 and 10 \( \mu \)m
- Deposition pattern inside the Cyclohaler using the simplified JKR model

**Images:**

- 1 μm (30 l/min)
- 2 μm (30 l/min)
- 5 μm (30 l/min)
- 1 μm (90 l/min)
- 2 μm (90 l/min)
- 5 μm (90 l/min)
Deposition along the inhaler:
Small particle deposit in the capsule chamber and on the grid
Larger particles deposit in the capsule and swirl chamber
Total deposition in the inhalers in dependence of particles size for different inhaler types, deposition models and flow rates.

Influence of deposition model and inhaler type.

It may be concluded that the drug particle deposition within the inhaler is the reason for the low efficiency.
Conclusions from the Present Analysis

- Aerosolisation of Clusters or Agglomerates by flow stresses is of minor importance !!!
- The motion of clusters within inhalers is strongly affected by wall collisions !!!
- Wall collisions are very effective for drug particle detachment from carriers (a Lagrangian model was developed to describe inertial detachment)

DEM simulations of carrier particle wall collisions

- However, during carrier wall collision drug particle deposition may occur: Model needed
- Also free moving drug particles deposit, depending on material and wall properties
- For describing cluster/agglomerate motion in inhalers the DPM is most suitable, i.e. particles are treated as an entity and relevant forces can be considered
- However, physical models are needed for drug detachment by flow and wall collisions
Further Studies on Schedule

- All developed models are implemented in OpenFOAM and will be further extended
- Implementation and testing of other deposition models (DMT-Derjagui-Muller-Toporev)
- Analysis of the influence of particle release position (consideration of a fixed capsule)
- Combined studies on Carrier Particle wall collisions and deposition
- Unsteady simulation of different breathing cycles; influence on released fine particle fraction; Comparison of different inhaler principles
- The COST Action initiated an interesting and important study which will be continued

➢ Thank you very much for your attention !!!