Chemical and Biological Engineering

Powder Fluidization in Dry Powder Inhalers

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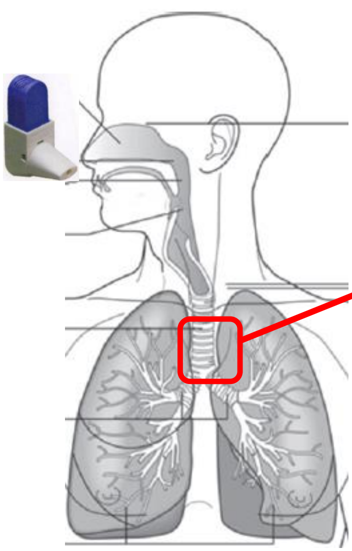
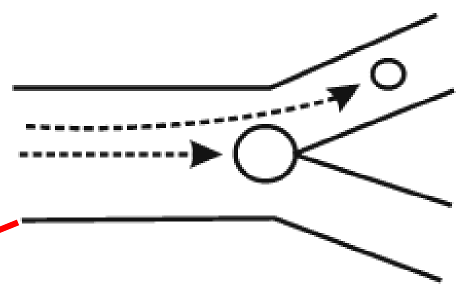
Session: Particle Technology in Product Design

Nov 20, 2020

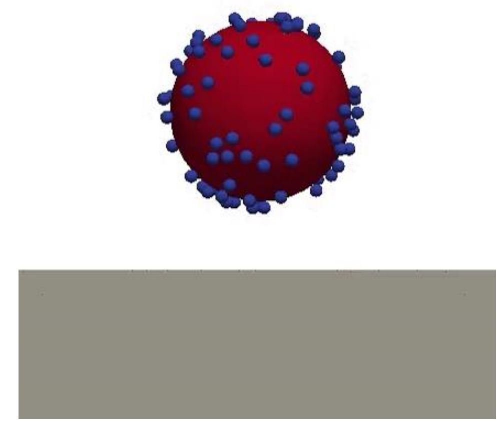
Overview

- Dry power inhalers (DPI) deliver active pharmaceutical ingredients (API) to human airways and lungs
- API particles are small (<5 μm), cohesive and hard to fluidize
- Larger lactose particles (~70 μm) are used as API carriers
- Inhalation fluidizes powder and releases API fragments
- Fragments smaller than 5 μm are delivered to lungs





Particles > 5 μm will deposit at turning or bifurcation of airway due to their large inertia [1]

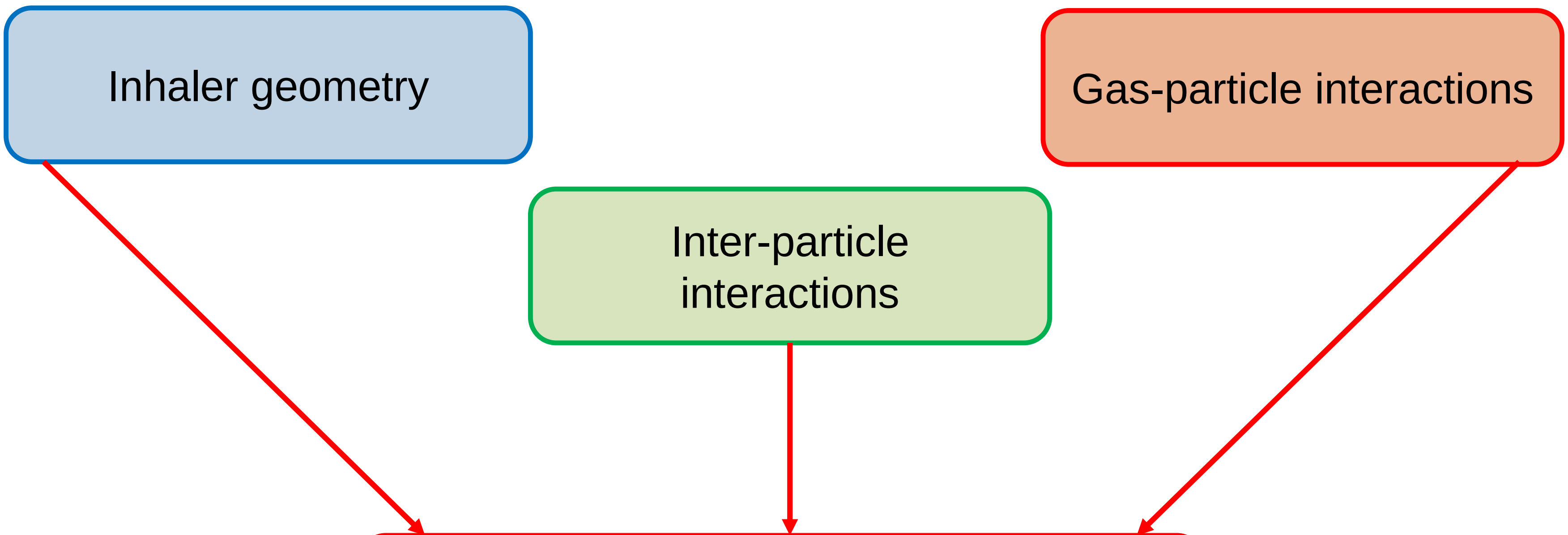


Deagglomeration due to wall-collision releases API

[1] Lee et al., *AAPS J.*, **11(3)**, 414 (2009)

Fine Particle Fraction

- The amount of drug delivered depends on the fraction of API released, characterized by **Fine Particle Fraction** (FPF)



$$FPF \equiv \frac{weight\ of\ API\ fragments < 5\mu\text{m}}{total\ weight\ of\ API\ particles}$$

[2] Tong et al., *Chem Eng J.* **164**, 432 (2010)

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Modeling Complex Particle Interactions in Dry Powder Inhaler Based Drug Delivery

Project funded by FDA U.S. FOOD & DRUG ADMINISTRATION

Project objectives

- Assemble a simulation platform to follow the transport of carrier and api particles (Accomplished ✓)
- Evaluate strategies to speed the computations up: track only representative api particles (Accomplished ✓) (Xiaoyu Liu's talk – same session)
- Explore how inter-particle forces affect release fractions through agglomerate-wall collisions and DPI simulations
- Validate the code and use it to assess effect of DPI device geometry on RF and FPF (Current talk)

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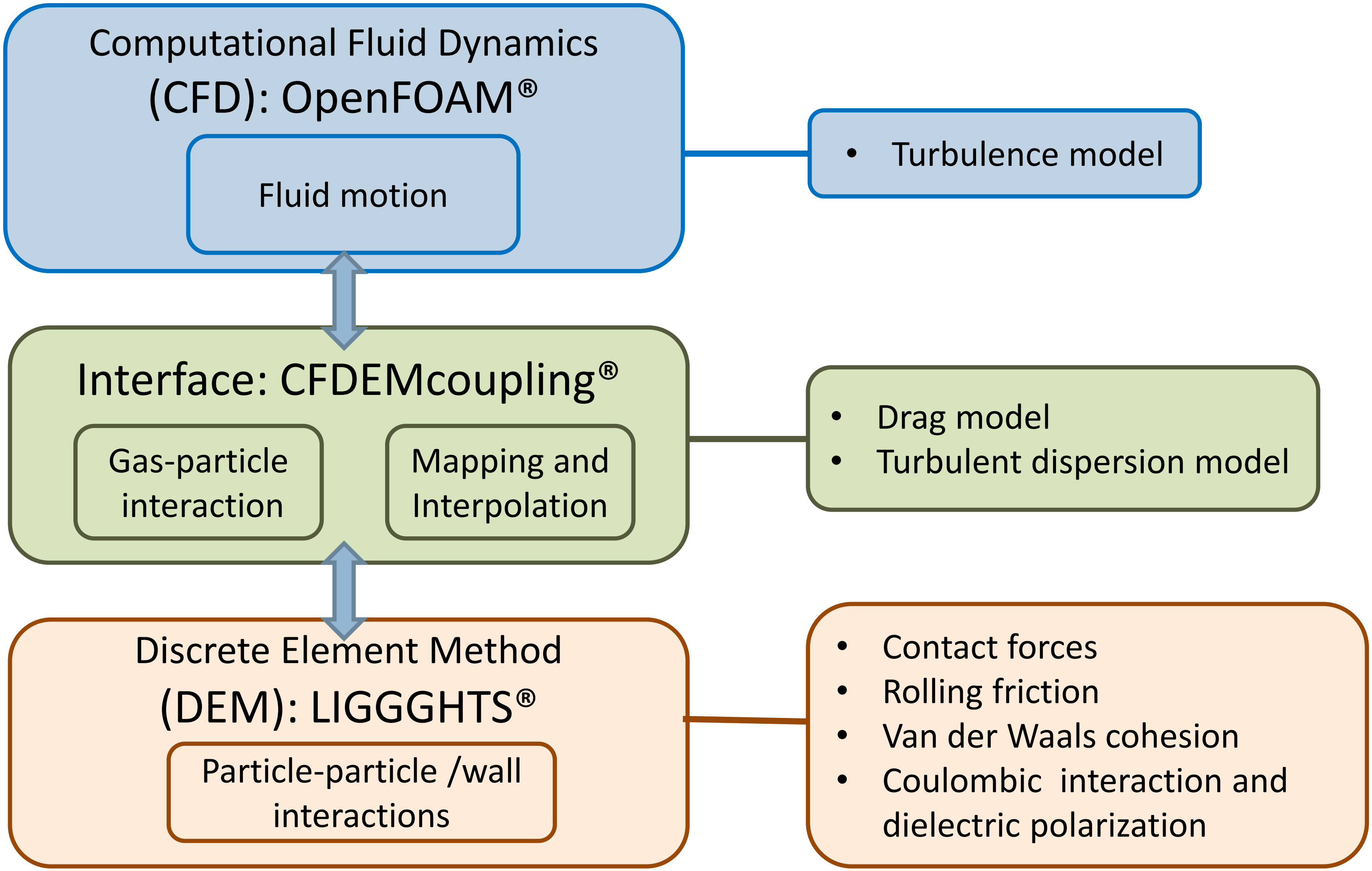
Presentation plan

- Numerical Method: CFD-DEM
- Validation: Comparison with experiments
- Effect of Initial conditions
- Effect of geometry
- Conclusion

Methodology



Code validation

Direct comparison with experiments

Measuring evacuation times:

- 5x5x300 mm channel
- Many flow rates $(9000 \leq Re \leq 23000)$
- Carrier only particles
- Diameter = 70 µm
- Number ≈ 0.5 M
- LES Dynamic Smagorinsky

Lactose powder fluidization in turbulent channel

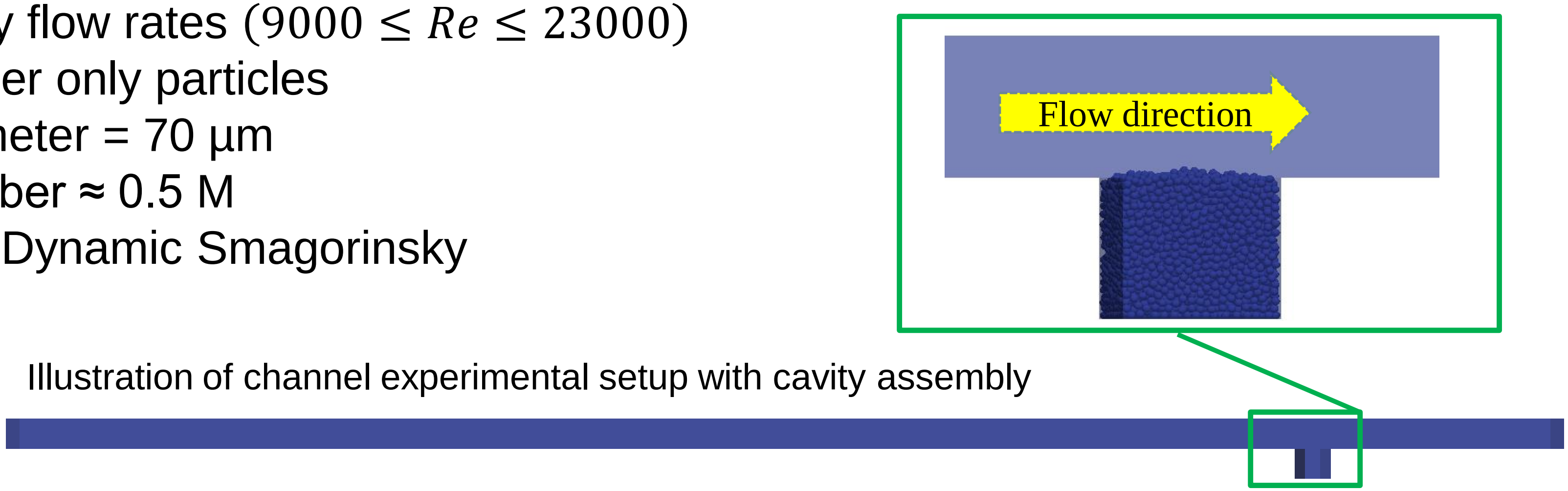


Illustration of channel experimental setup with cavity assembly

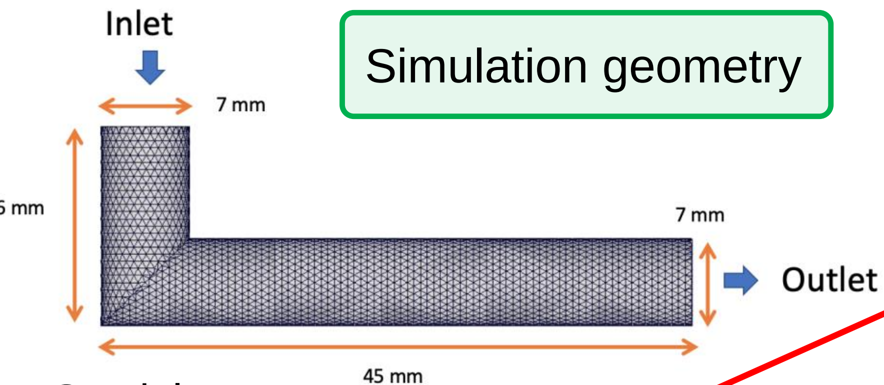
Powder emptying times

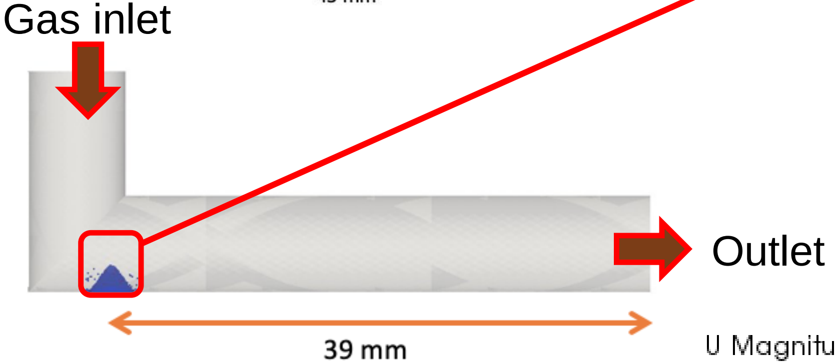
	Re =18500	Re =20300	Re =22500
Experimental time [s] *	0.47	0.406	0.346
Simulations time [s]	0.48	0.36	0.326

* Mahmoudi, S., et al. *Experimental Thermal and Fluid Science* 103 (2019): 201-213.

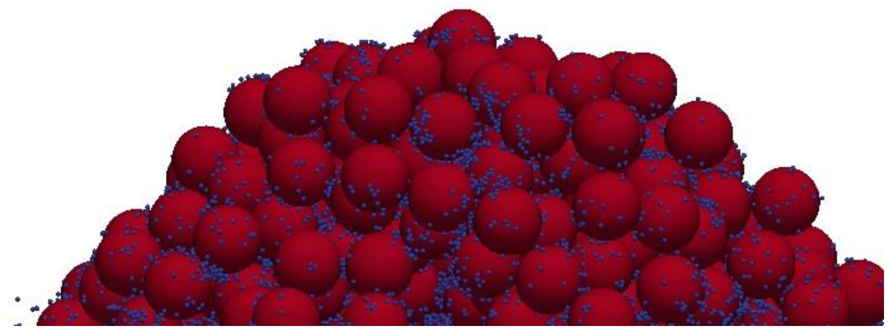
Initial conditions sensitivity: effect of dose loading

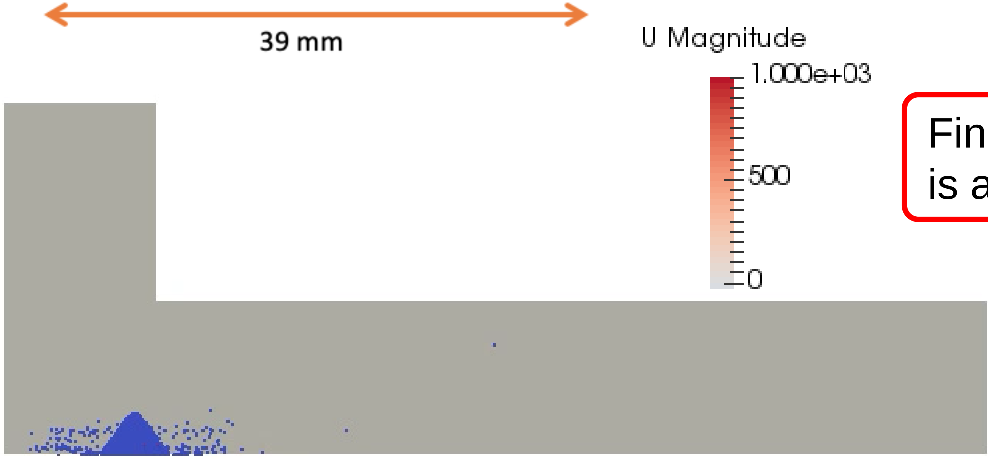
Simulation geometry





Carrier (70 μm) and **API** (5 μm) particles are inserted and allowed to agglomerate and settle in this region
Dosage = 3.5mg





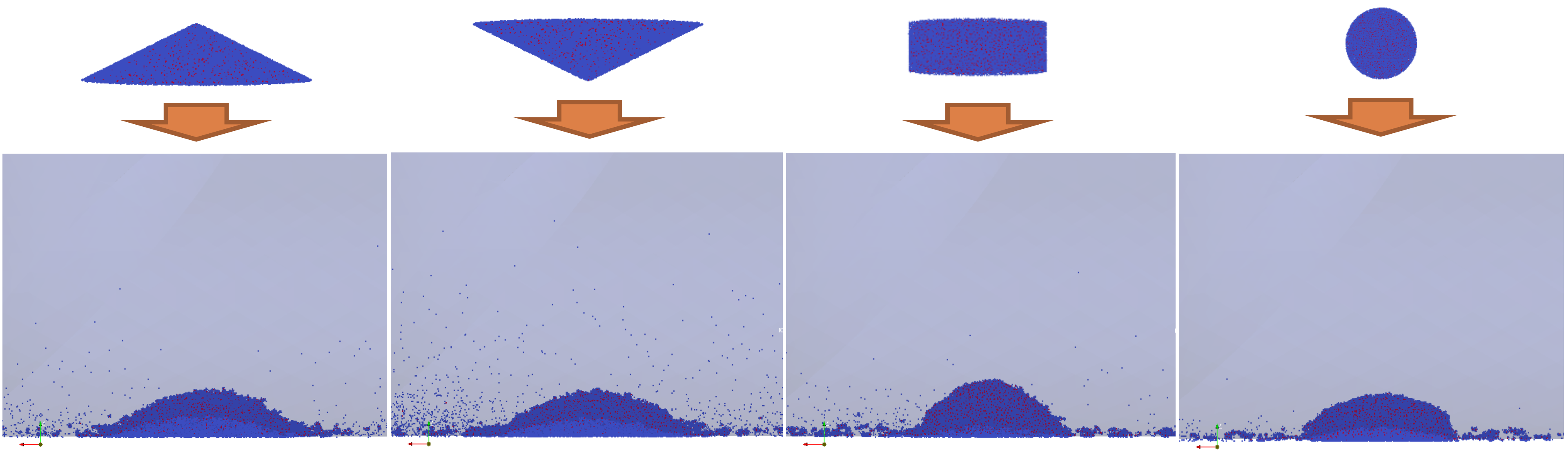
Fine particle fraction is analyzed at outlet

[3] Nguyen et al., Int J Pharmaceut, 57, 31 (2018)
[4] van Wachem, et al. *AIChE Journal* 63.2 (2017): 501-516.

Initial conditions sensitivity: effect of particles settling

3.5 mg dose: 13,000 carrier particles and 150,000 representative api particles

Case 1 **Case 2** **Case 3** **Case 4**



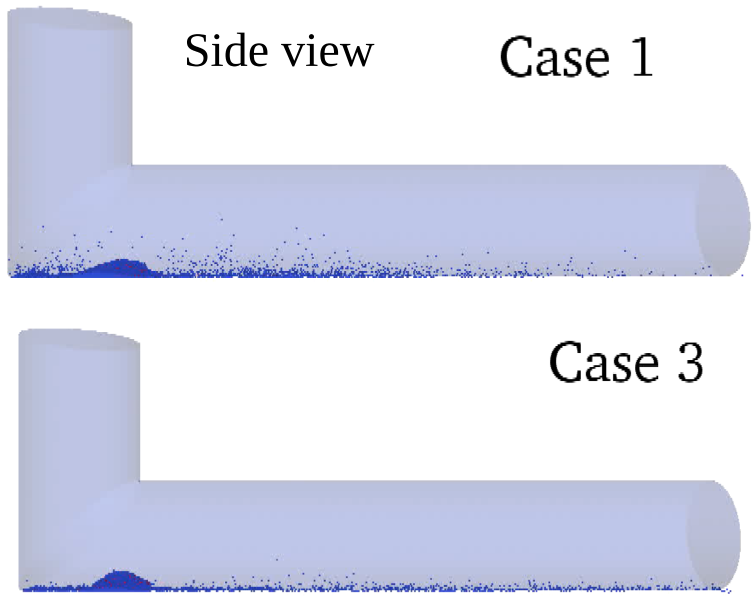
Stats of coupled CFD-DEM simulations

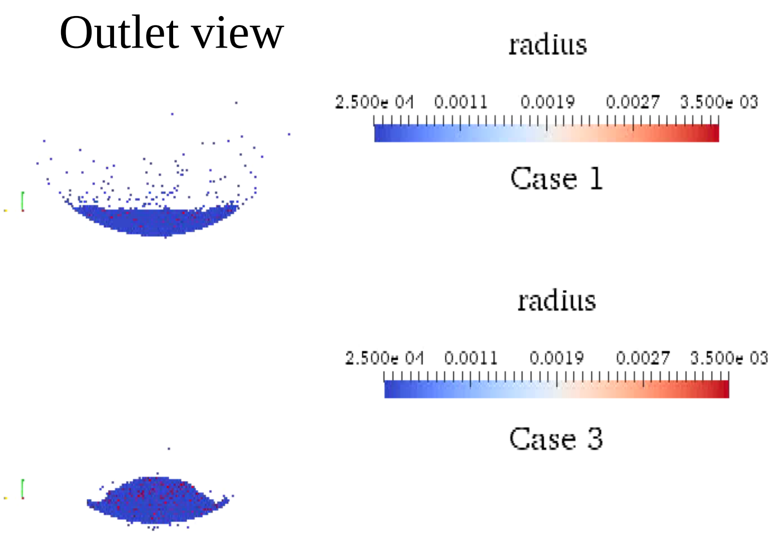
	Case 1	**Case 2**	**Case 3**	**Case 4**
Released API Fraction	0.412	0.407	0.190	0.336
Fine Particle Fraction	0.285	0.288	0.109	0.235

Initial conditions sensitivity: effect of particles settling

Macroscopic dynamics

- Drag force on pile is affected by its initial shape
- Flatter pile gets defragmented more easily
- Small fragments undergo more wall collisions
- Smaller fragments spend more time in the inhaler than the bigger ones

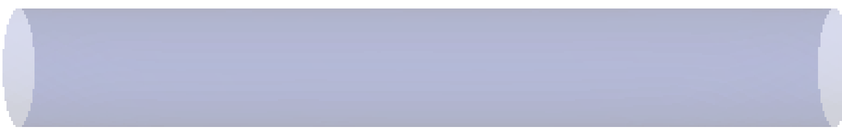




Effect of device geometry on the fine particle fraction

How could the device geometry be modified to enhance wall collisions?

Geometry A



Geometry B

Geometry C

Geometry D

Geometry E

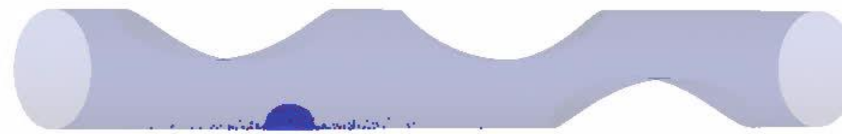
Geometry F

Effect of device geometry on the fine particle fraction

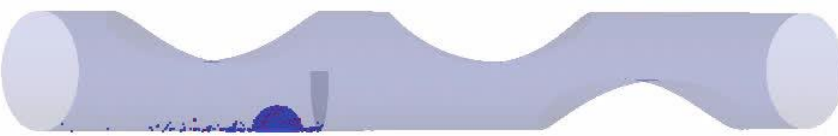
How could the device geometry be modified to enhance wall collisions?

Geometry A FPF = 7%

Geometry B FPF = 70%

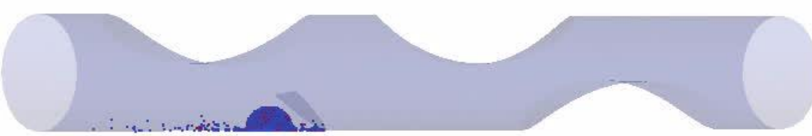


Geometry C FPF = 71%

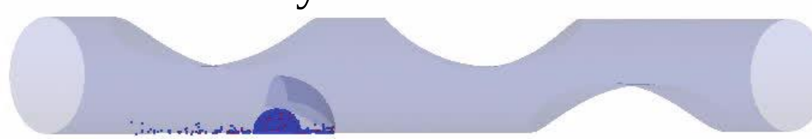


Geometry D FPF = 59%

Geometry E FPF = 68%

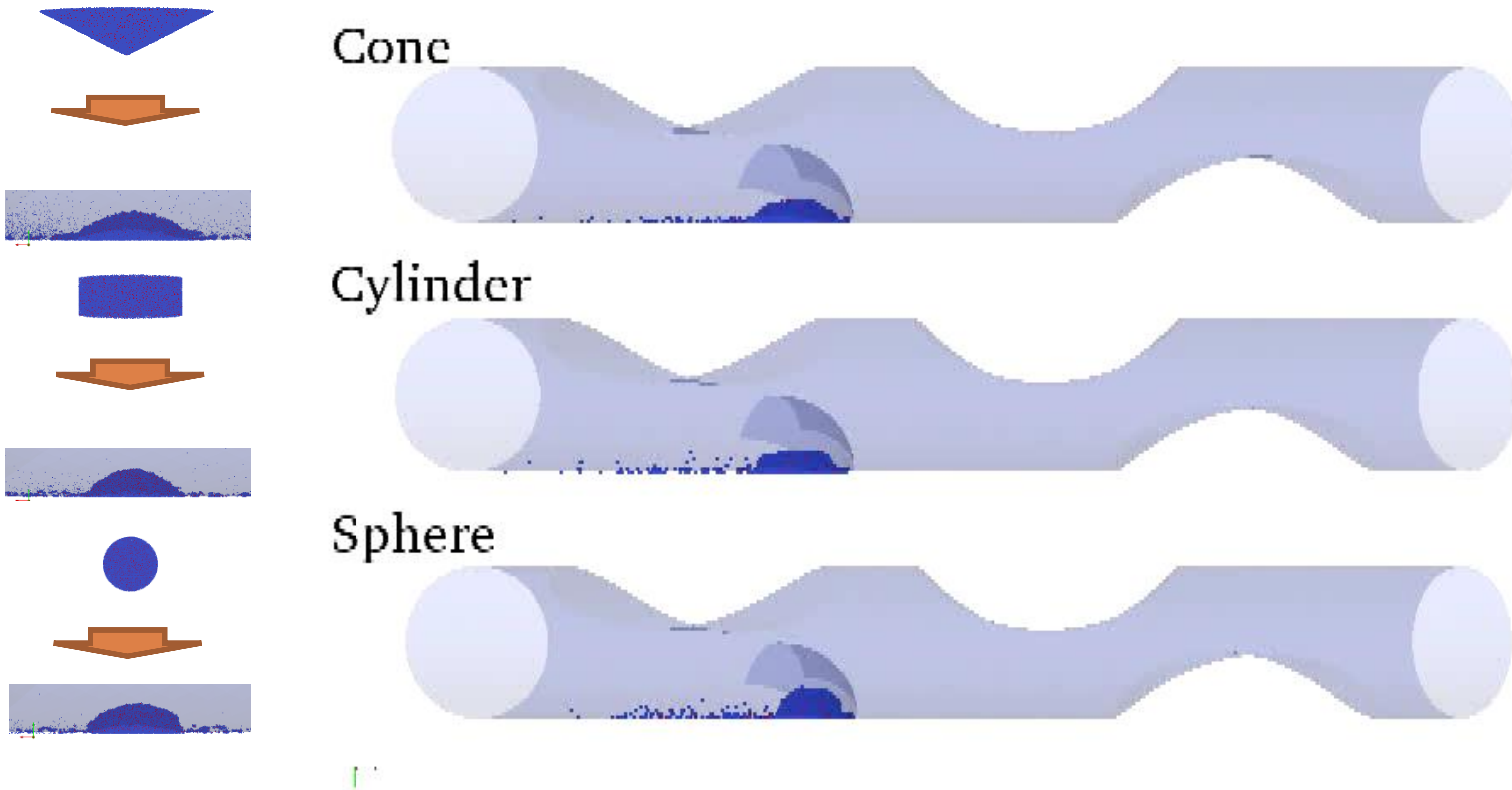


Geometry F FPF = 88.1%



Effect of device geometry on the fine particle fraction

Probing the initial conditions effect with the modified device geometry and their effect on the FPF



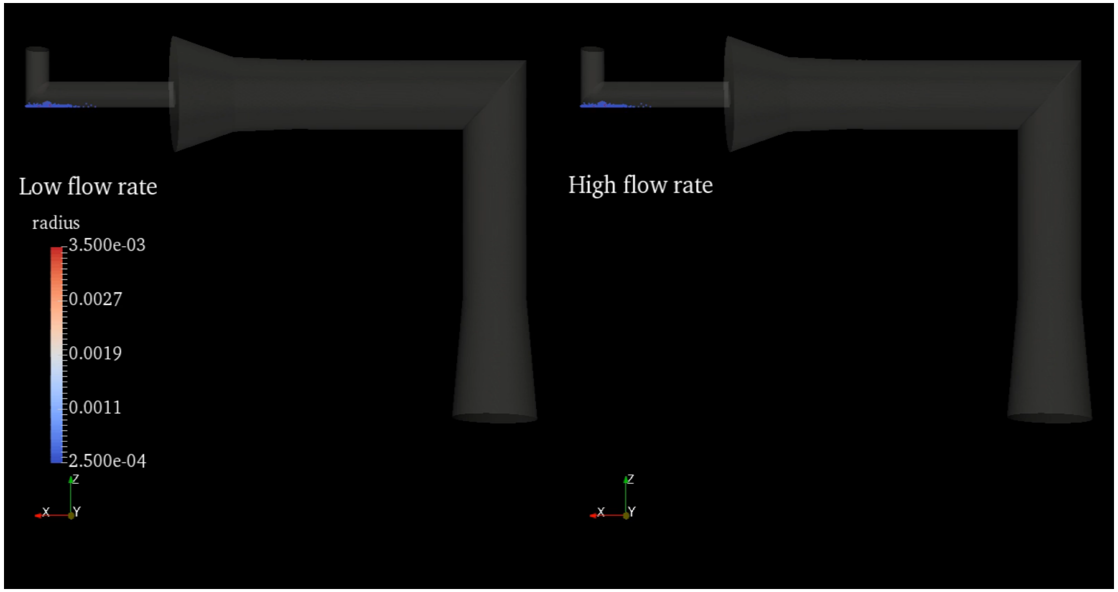
FPF ~ 88%

FPF ~ 87.2%

FPF ~ 86.9%

Summary

- CFDEM code was validated against experimental data
- Dose loading method was found to affect the FPF in simple DPI geometry
- Device geometry modifications can significantly enhance agglomerate wall collisions, leading to larger FPF and decreased sensitivity to dose loading method



Acknowledgement

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