Modeling Complex Particle Interactions in Dry Powder Inhaler

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Session: Particle Technology Forum (03)
Particle Technology in Product Design
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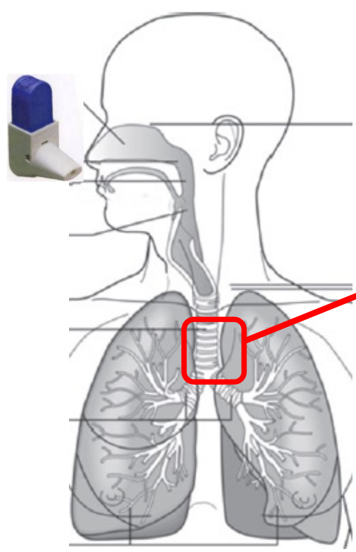
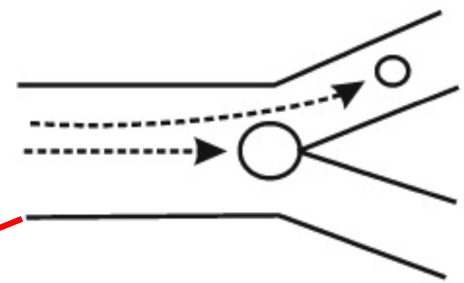
U.S. FOOD & DRUG ADMINISTRATION

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 ~ 100 μm) are used as carrier
- Inhalation fluidizes powder and releases API fragments
- Fragments smaller than 5 μm are delivered to lungs



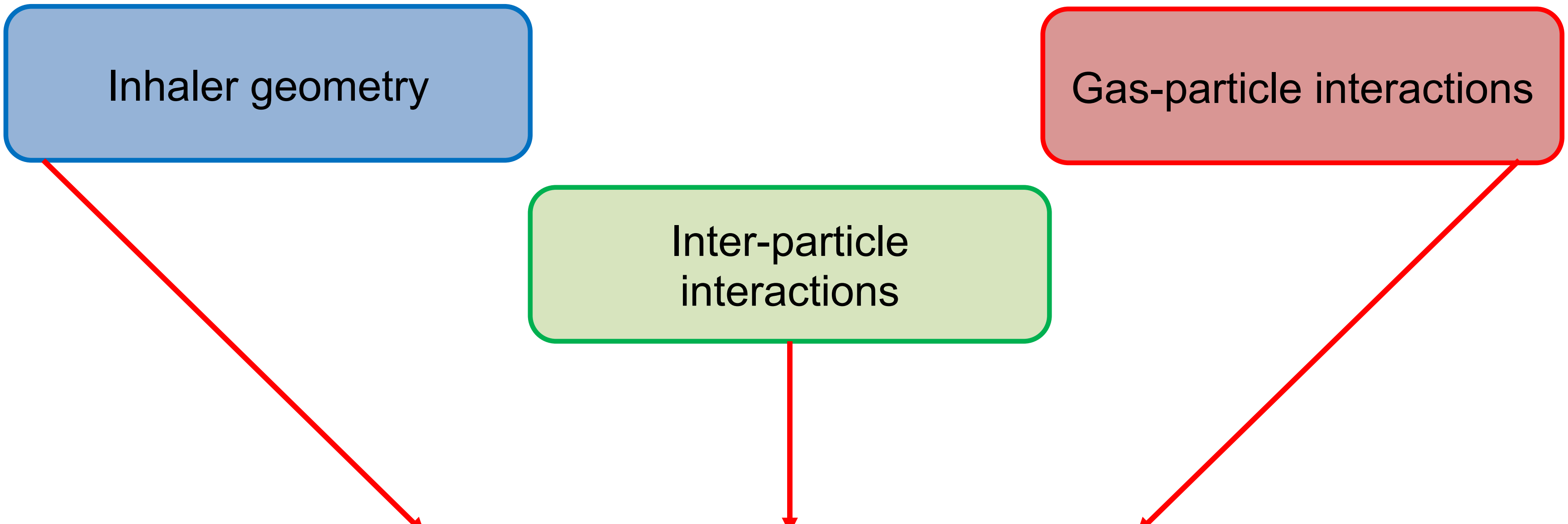


Particles > 5 μm will deposit at turning or bifurcation of airway due to their large inertia

[1] 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)

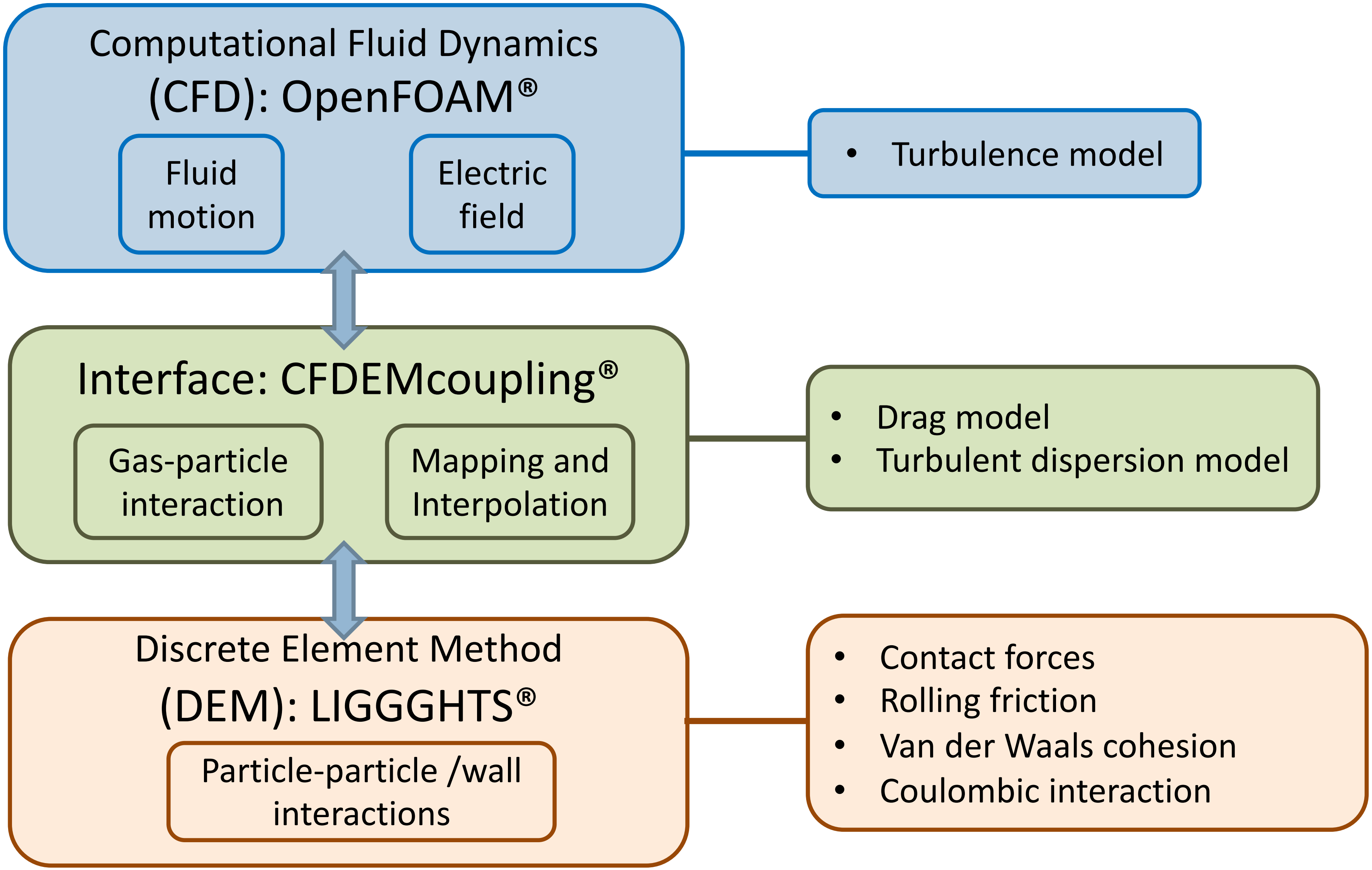
Modeling Complex Particle Interactions in Dry Powder Inhaler Based Drug Delivery

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

Project objectives

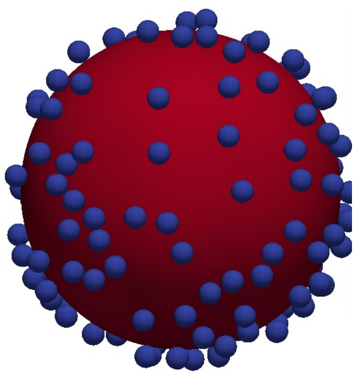
- Assemble a simulation platform to follow the transport of carrier and api particles (Accomplished ✓)
- Evaluate strategies to speed the computations up: track only representative api particles (Accomplished ✓) (**Current talk**)
- Explore how inter-particle forces affect release fractions through agglomerate-wall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

Methodology: CFD-DEM



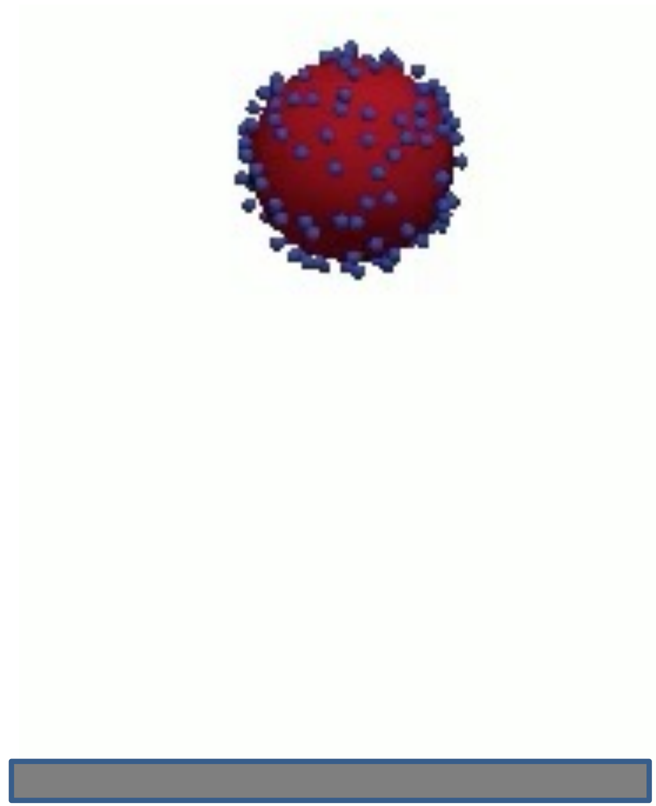
Agglomerate-wall collision simulation

Type	Diameter	Number	Vol %
API	5µm	130	4.5
Carrier	70µm	1	95.5



An agglomerate is formed with either
- Van der Waals cohesion (Hamaker model)
- or electrostatic interaction (assigning opposite charges to carrier and API)

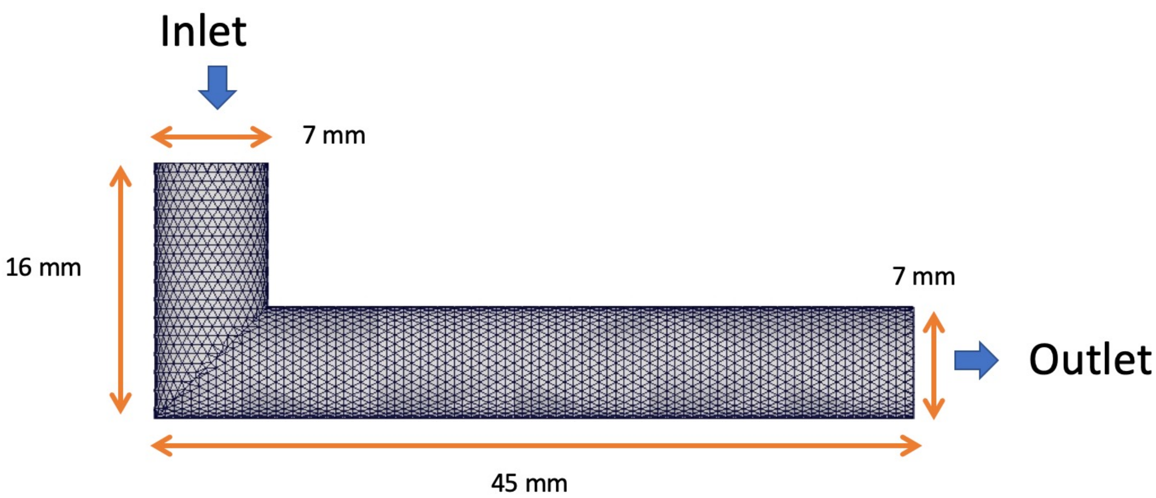
10 different initial configurations



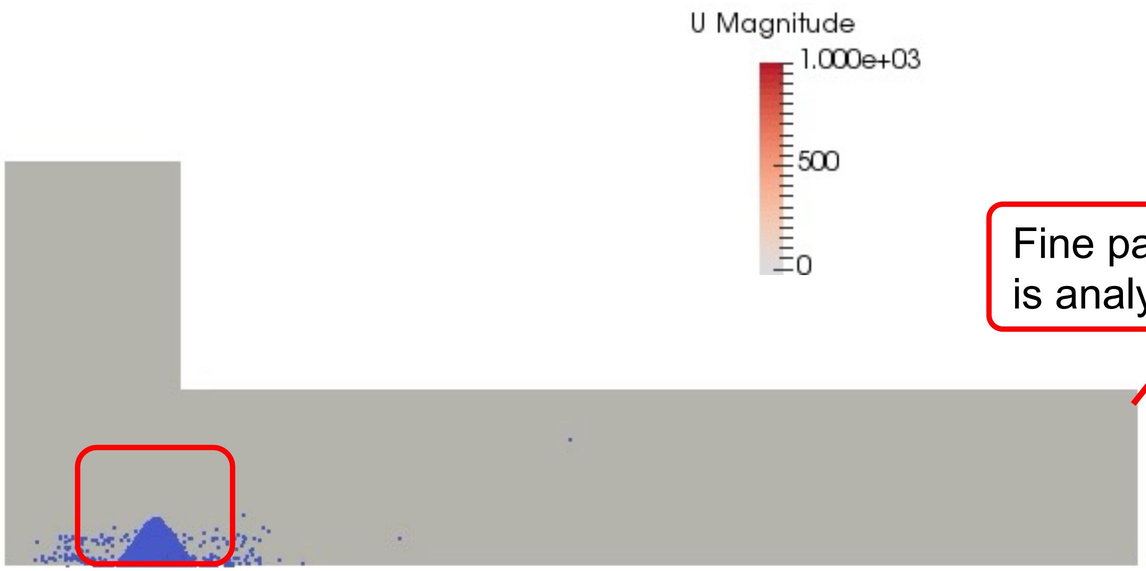
Collide the agglomerate with a wall and analyze FPF and release fraction

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

Screen-haler simulation



Carrier (70 μm, 4k)
API (5 μm, 520k)
Dosage = 1mg

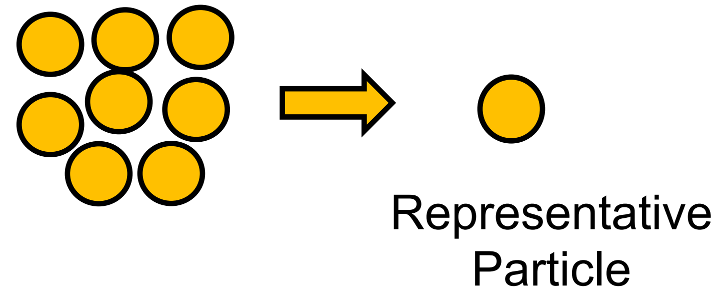


Fine particle fraction is analyzed at outlet

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

Coarsening Approach: representative particle

Particle-based coarsening approach:
- Model API particles by "representative particles", each representing N primary API particles (N is the **coarsening factor**)

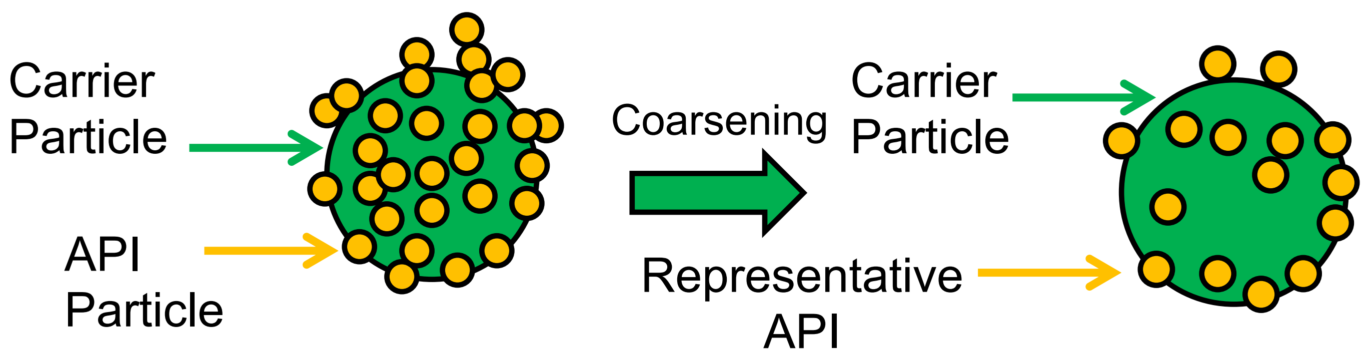


$$N_i m_i \frac{d\boldsymbol{v}_i}{dt} = \mathbf{max}(\boldsymbol{N_i}, \boldsymbol{N_j})\, f_{ij}(\boldsymbol{x}_i, \boldsymbol{x}_j) + N_i \boldsymbol{f}_i^d$$

N_i, N_j: numbers of primary particles in representative particle i and j respectively

f_{ij}: interaction force between two primary particles i and j

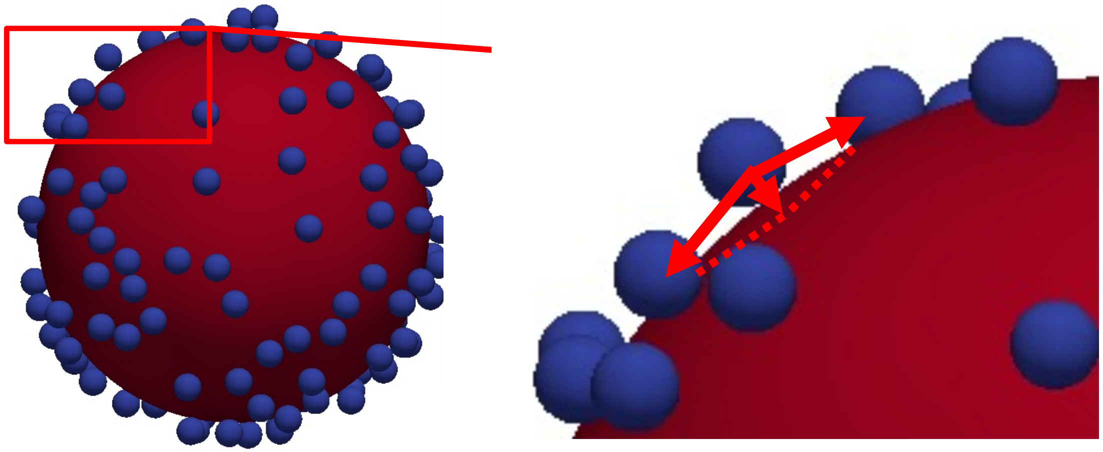
$\boldsymbol{f}_i^d$: drag force experienced by one primary particle i



The current model uses
- N = 1 for carrier particles (no coarsening)
- N ≥ 1, same N for API particles.

This approach reduces computational cost as fewer particles are tracked in the simulation

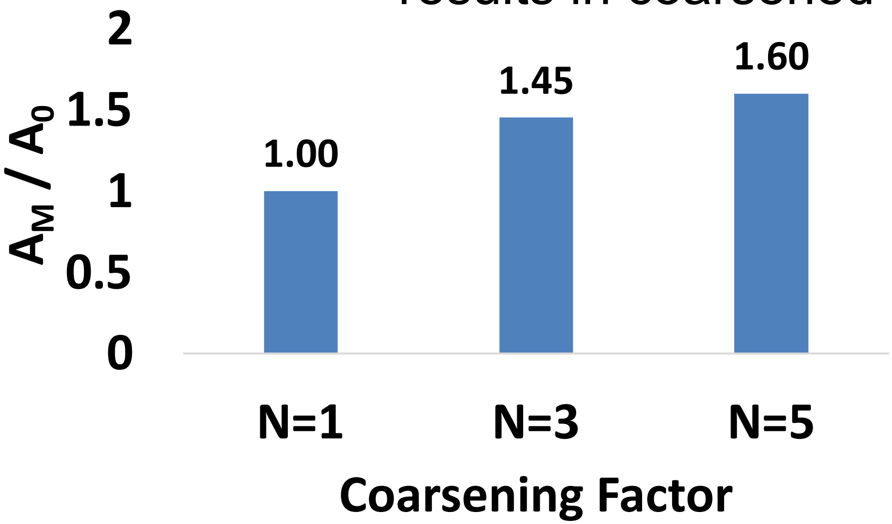
Coarsening correction



Cohesion among API particles constitutes an additional attractive force between carrier and API.

=> This effect can be corrected to ensure consistent results in coarsened cases

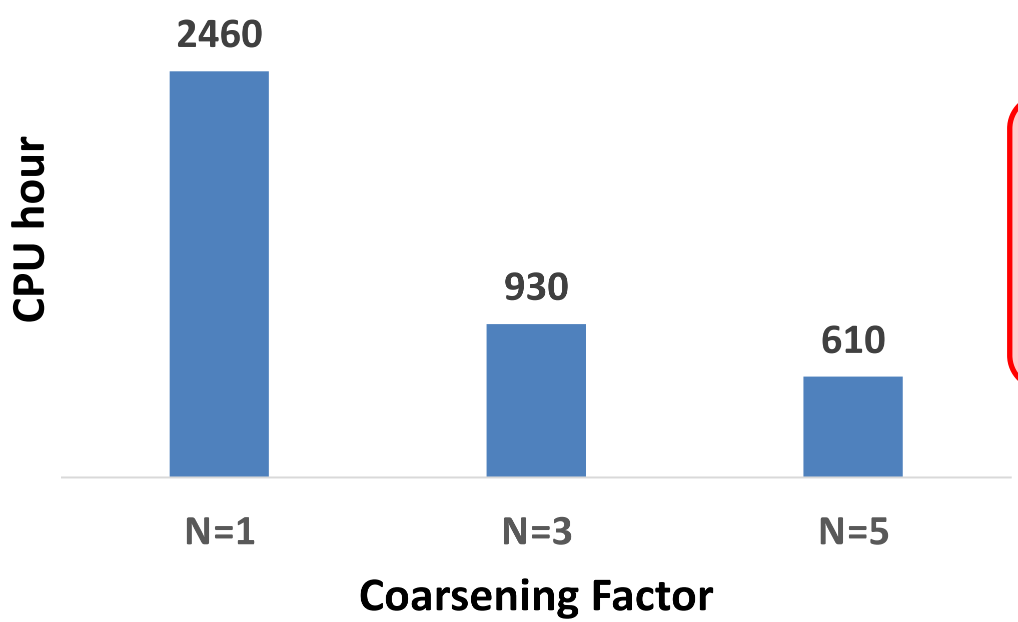
These corrections can be tuned using short agglomerate-wall collision test.



The ratio of modified Hamaker constant Ha_M to original Hamaker constant Ha_0 for different coarsening factors

Screen-haler simulation results

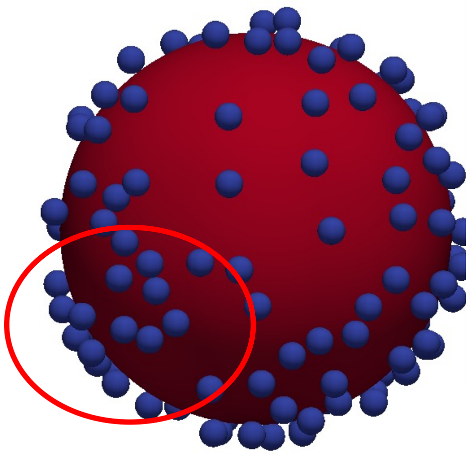
	Coarsening Factors		
	1	**3**	**5**
FPF	0.585	0.594	0.560
Release	0.751	0.709	0.691



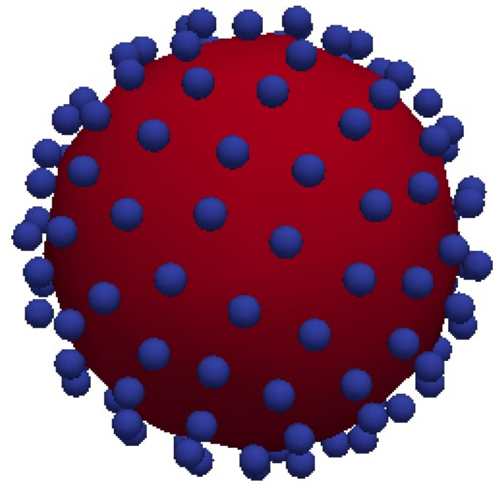
Consistent FPF can be obtained using coarsened simulation with low computation cost

Nature of particle interaction

Van der Waals' cohesion
(always attractive)



Electrostatic interaction
(attractive between API and carrier, repulsive among API)



Binary systems of particles tend to pick up opposite charges

API particles may cluster on the carrier surface

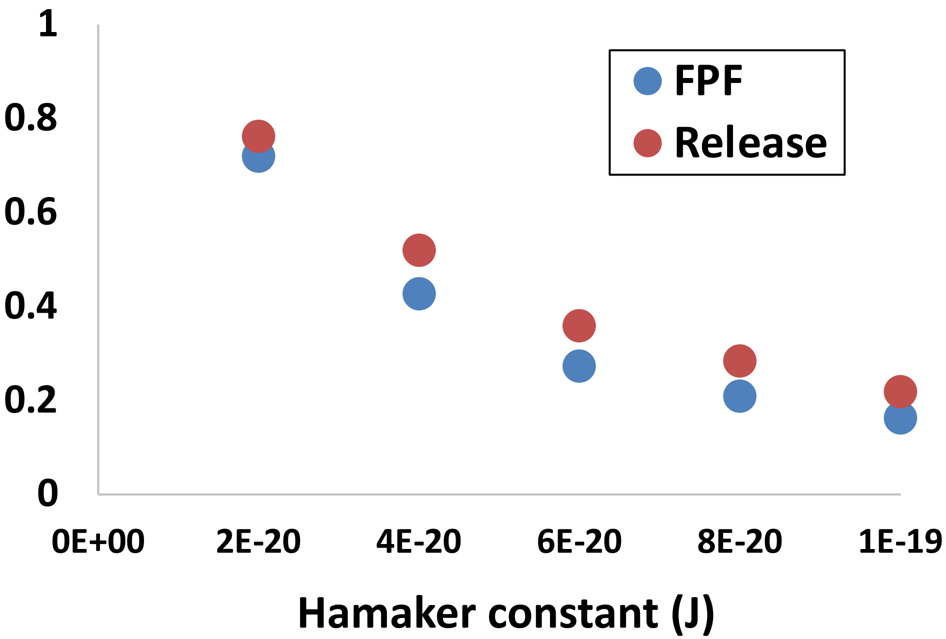
API particles maximize separation with other API particles due to repulsion

Different agglomerate configurations between VDW cohesion and electrostatic interaction

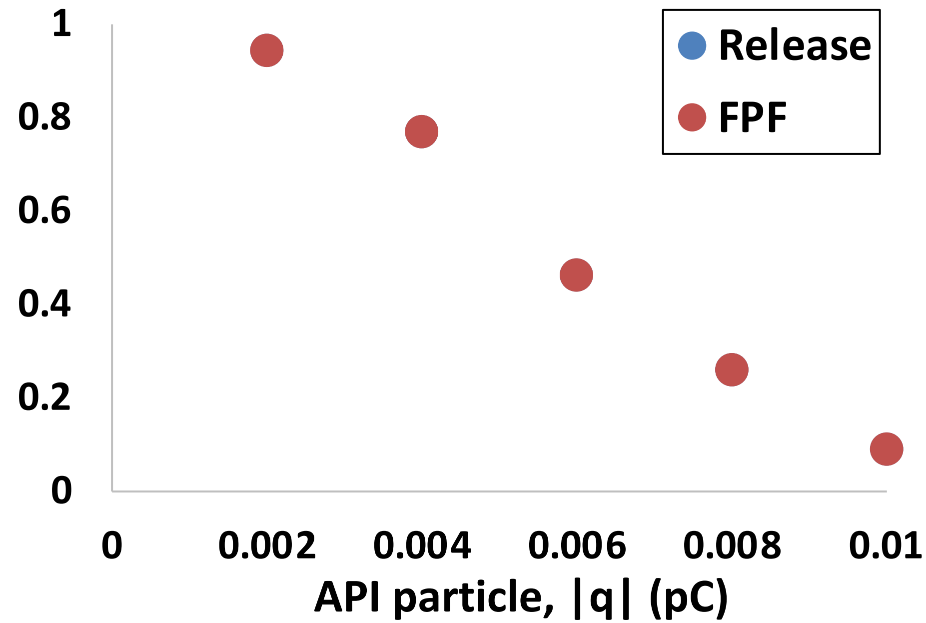
[5] Yu et al., Pharm Res, 34(08), 1707 (2017).

Agglomerate-wall collision

Van der Waal's cohesion
(always attractive)



Electrostatic interaction
(attractive between API and carrier, repulsive among API)



Impact velocity = 0.5m/s

Some API may be released as API-agglomerate

All API are released as singlet

Summary

- We have developed a CFD-DEM code for simulating dry powder inhaler

- We formulated a representative particle approach that saves computational cost and implemented correction to ensure consistent result

- As VDW cohesion and electrostatic interaction increases, fewer API get released.
  - VDW cohesion: some API may be released as API-agglomerate
  - Electrostatic interaction: all API are released as singlet

Acknowledgement

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