

Considerations for CFD-DEM Predictions of Regional Deposition Following Dry Powder Inhalation Administration

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Generic Orally Inhaled Drug Products (OIDPs)

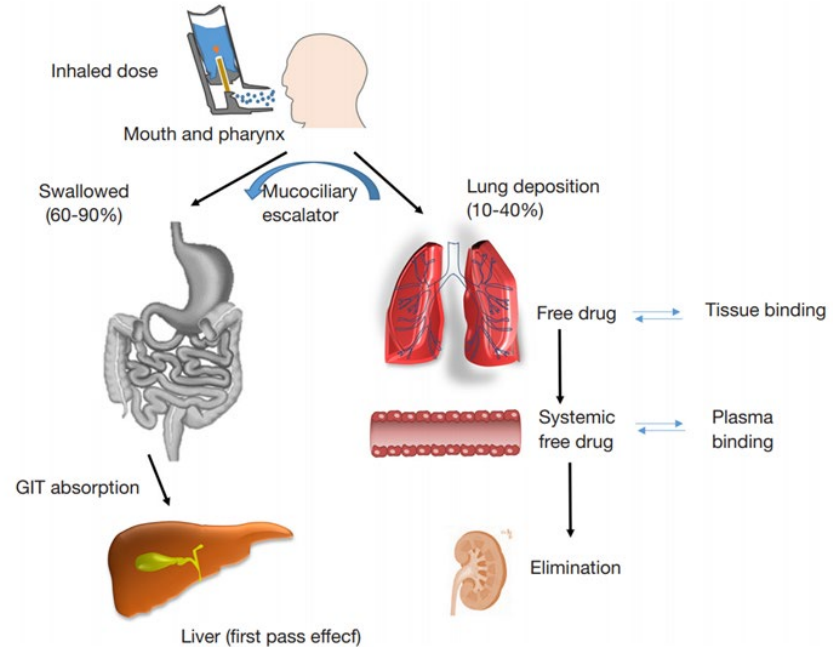


- Association of Accessible Medicines¹: Generic drugs produced \$265 billion in savings in the U.S. in 2017. However, no approved generic drug products for complex drug-device combination OIDPs on market.
- Since 2017, only a few generic OIDPs have been approved in the U.S., affecting 27 million in the U.S. with asthma² and 16 million with COPD³.
- Challenges in product development and manufacturing due to cost and time while passing all FDA-recommended studies in demonstrating bioequivalence (BE) to the reference **listed drug** product.

Bioequivalence (BE) at the Site of Action



- For locally acting OIDs, lung tissue is the site of action.
- Regional deposition is upstream of local tissue drug exposure and systemic pharmacokinetics (PK) is downstream.



Drug delivery, absorption, distribution, metabolism, and elimination of OIDs (Figure from de Pablo et al.⁴)

Weight of Evidence Approach for ODPs

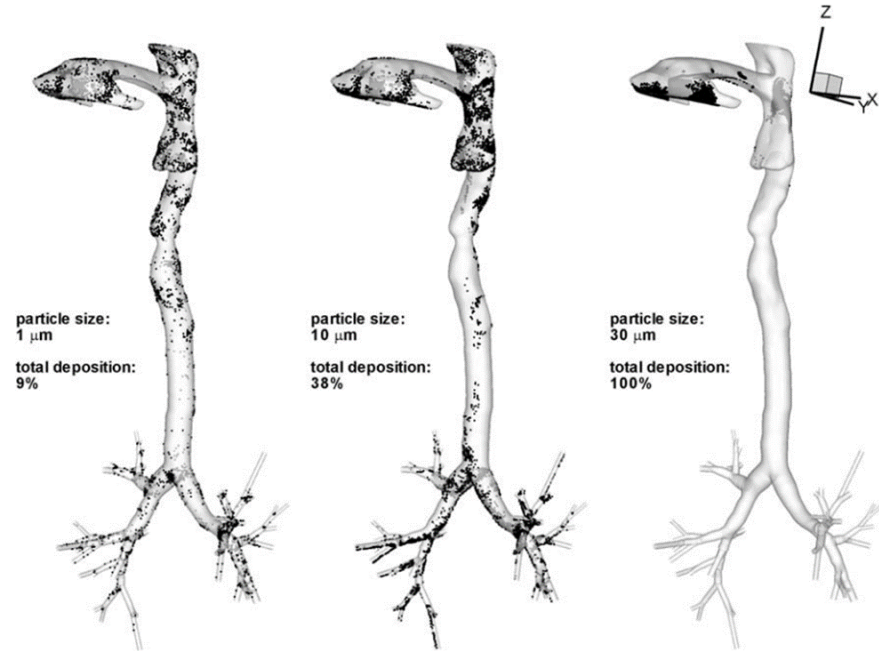
BE recommendations from the U.S. Food and Drug Administration (FDA) include in vitro studies, in vivo studies, and formulation and device sameness for metered dose inhalers (MDIs) and dry powder inhalers (DPIs)

In vitro studies	In vivo studies
❖ Single actuation content (MDIs and DPIs) ❖ Aerodynamic particle size distribution (APSD) (MDIs and DPIs) ❖ Spray Pattern (MDIs only) ❖ Plume Geometry (MDIs only) ❖ Priming and Repriming (MDIs only)	❖ Comparative PK with fasting, two-way crossover design in healthy subjects (MDIs and DPIs) ❖ Comparative Clinical Endpoint or Pharmacodynamic (MDIs and DPIs)

Utility of Regional Deposition CFD Modeling as an Alternative BE Approach

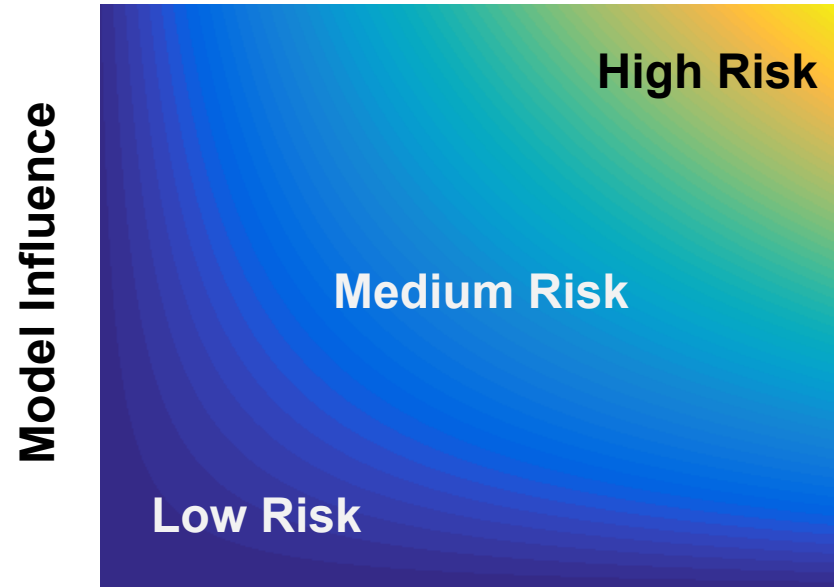


- Prediction of fluid and particle transport
- Allows for consideration of realistic geometries
- Can consider effect of input plume geometry as well as particle size distribution (PSD)
- Help predict how regional deposition may be affected by disease state
- Aid in product development and in justifying deviations in product performance and formulation from the RLD, especially for non-Q1 (qualitative)/Q2 (quantitative) formulations



Model Credibility – ASME V&V 40 Concepts

- American Society of Mechanical Engineers (ASME) Verification & Validation 40 standard⁶
- Context of Use: Describes what question the model addresses and to what extent
- Model Risk: Determined by decision consequence and model influence
- Credibility: Verification and Validation



Decision Consequence

(Figure from Walenga et al.⁷)

Regional Deposition Validation



- Deposition should be predicted in all lung regions (especially, central and peripheral).
- Lung region definition should be supported by in vivo data and clinical understanding.
 - Complementary model may be needed for small airways if CFD is used for regional deposition predictions of upper airways.
- Preferred source of comparator data is in vivo imaging data via either gamma scintigraphy or single photon emission computed tomography (SPECT)/computed tomography (CT)

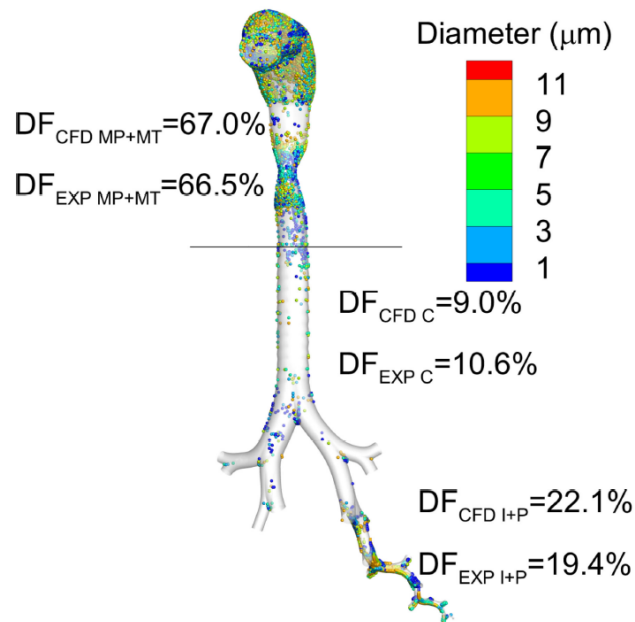


Figure 6 from Tian et al.⁸ – Predictions of regional deposition fraction (DF) (mouthpiece (MP), mouth-throat (MT), central (C), intermediate (I), and peripheral(P)) for DPI, as compared with in vivo gamma scintigraphy data.⁹

Dry Powder Inhalers (DPIs)

- Typically deliver aerosol based on patient effort
- Often use larger carrier particles to improve aerosolization of smaller active pharmaceutical ingredient (API) particles
- Many different designs including capsules, a reservoir, or blisters



Figure 5 from Myers¹⁰ and Gardenhire et al.¹¹ – various DPI designs

Carrier-API Particle Interactions in Dry Powder Inhalation



- CFD-only models typically considers particles as point masses
 - Cannot consider complex carrier-API particle interactions for DPIs
- Discrete element method (DEM) modeling can consider complex particle interactions
- May be paired with CFD

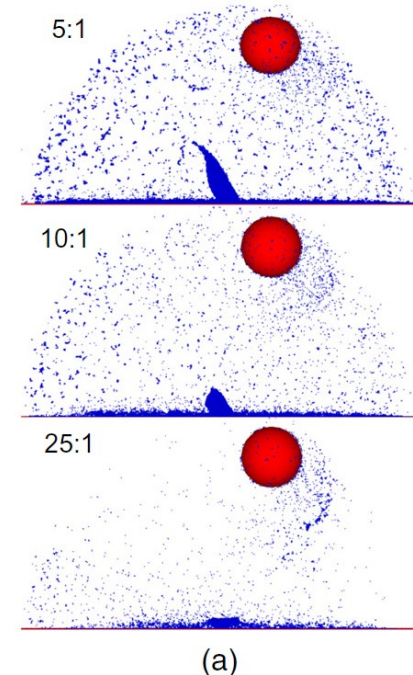
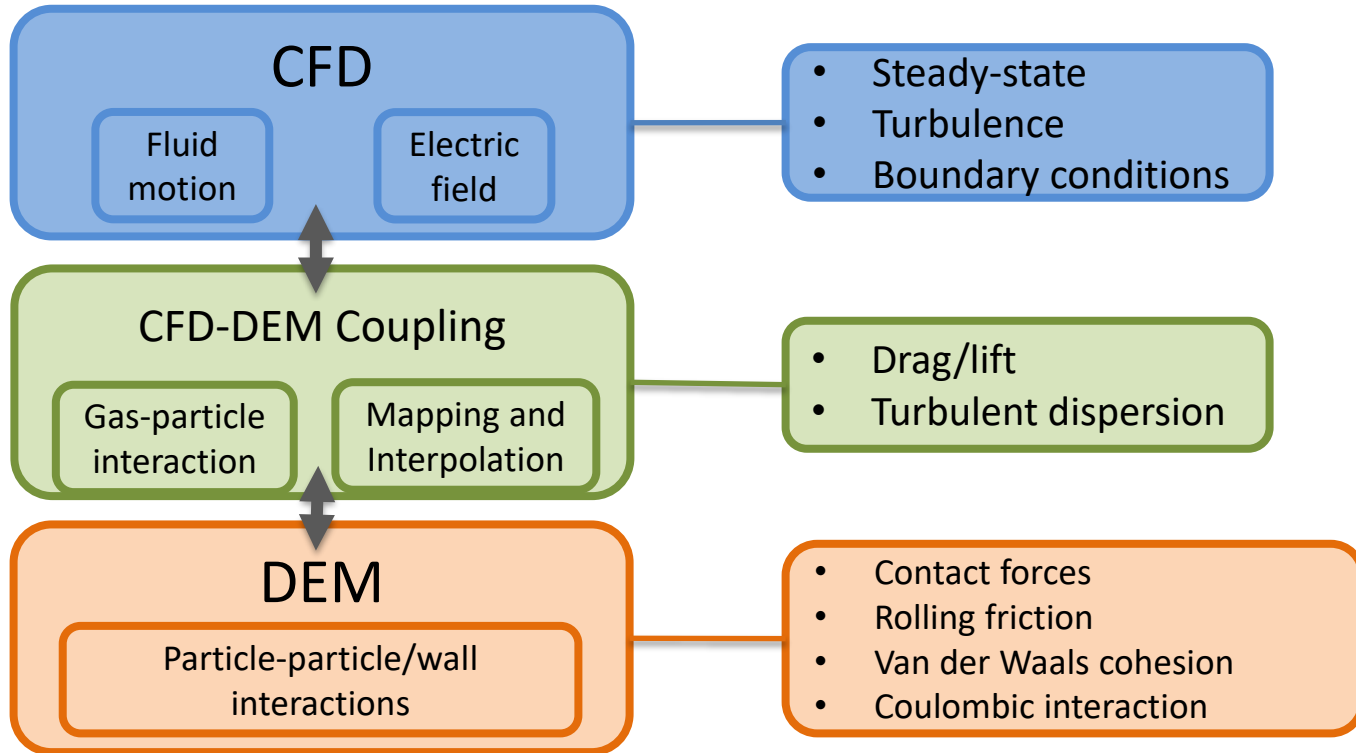


Figure 4(a) from Tong et al.¹²

CFD-DEM Coupling



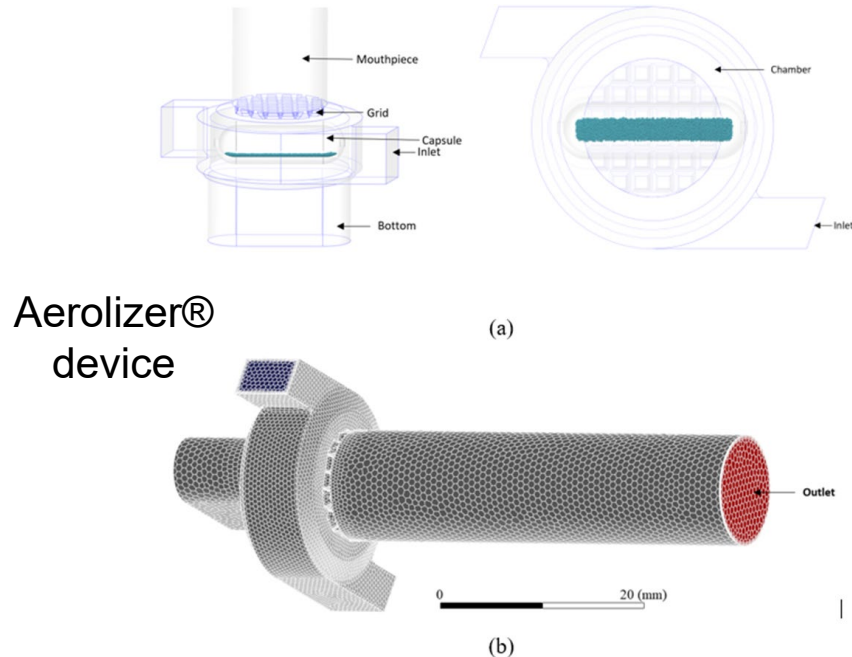
Additional Considerations for CFD-DEM Models



- CFD-DEM models are promising, and future directions may include addressing considerations to ensure the performance and accuracy of the model, such as (but not limited to):
 1. Aperture size (for capsule-based formulations)
 2. Particle shapes
 3. Device geometry
 4. Realistic particle size distribution (micronized carrier particles)

Capsule Aperture Effect

Properties are chosen to be similar to previous work by Tong et al. (2013)



Parameter	Value
Number of particles (N_p)	10000
Total powder mass (μg)	5.92×10^{-3}
Particle size distribution (micron)	60-140
Particle density (kg/m^3)	1590
Particle-particle sliding friction	0.25
Particle-wall sliding friction	0.25
Young's Modulus (Pa)	1×10^7
Poisson's ratio	0.29
Particle-particle Ha (J)	8.2×10^{-20}
Particle-wall Ha (J)	7.7×10^{-20}
Flow rate (L/min)	90
Rotating speed (rpm)	4050
Aperture diameter (mm)	0.7, 1.0, 1.3, 2.5, 4.0

Figure 1. (a) Front and top views of the device with initial powder state (highlighted in teal);

Effect of Aperture Size on Fluid Flow

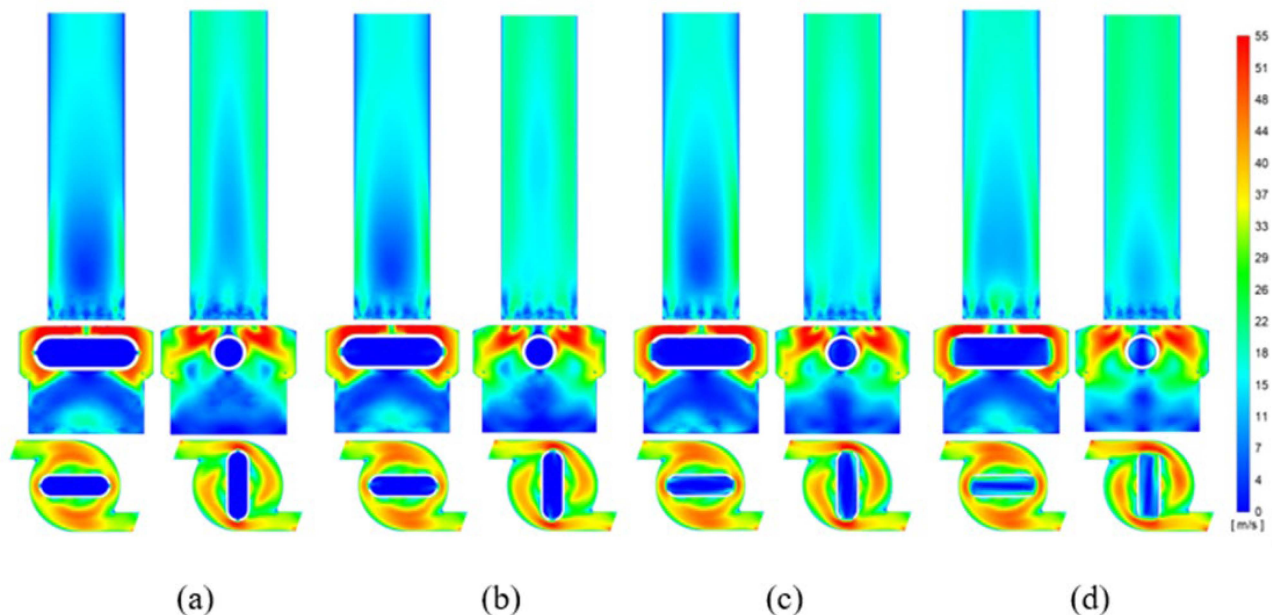


Figure 3. In plane flow velocity magnitudes at 7.4 ms and 11.2 ms, respectively, with different aperture sizes: (a) 0.7 mm; (b) 1.3 mm; (c) 2.5 mm; and (d) 4.0 mm.

Emptying Visualization

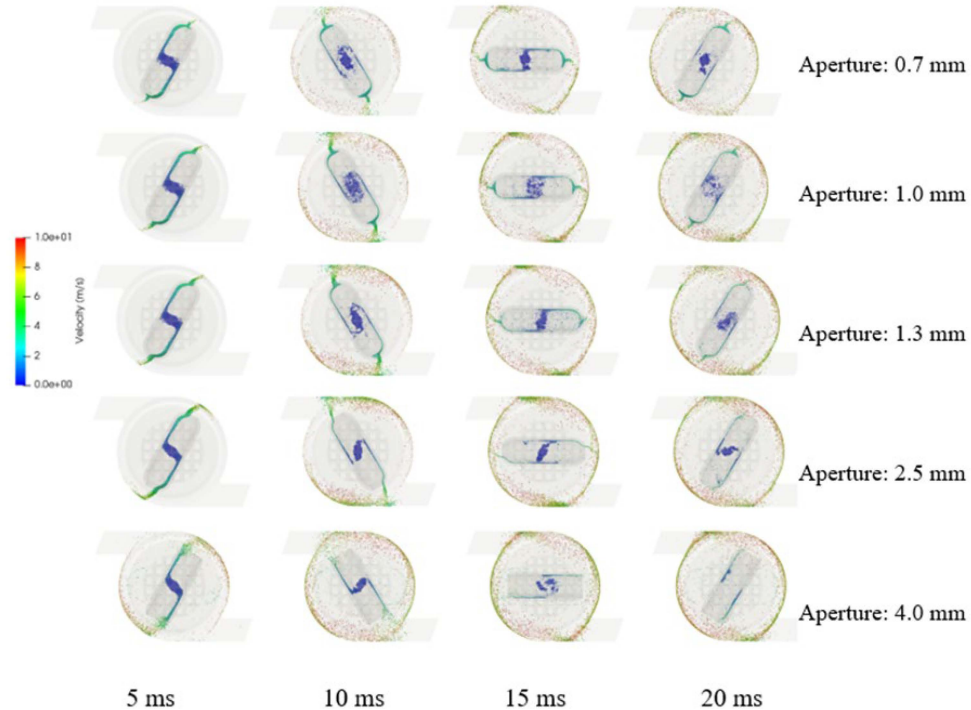


Figure 4. Snapshots of particle evacuation from capsule with various aperture sizes and at different times (clockwise rotation). Colour represents particle velocity magnitude.

Particle Evacuation Rate

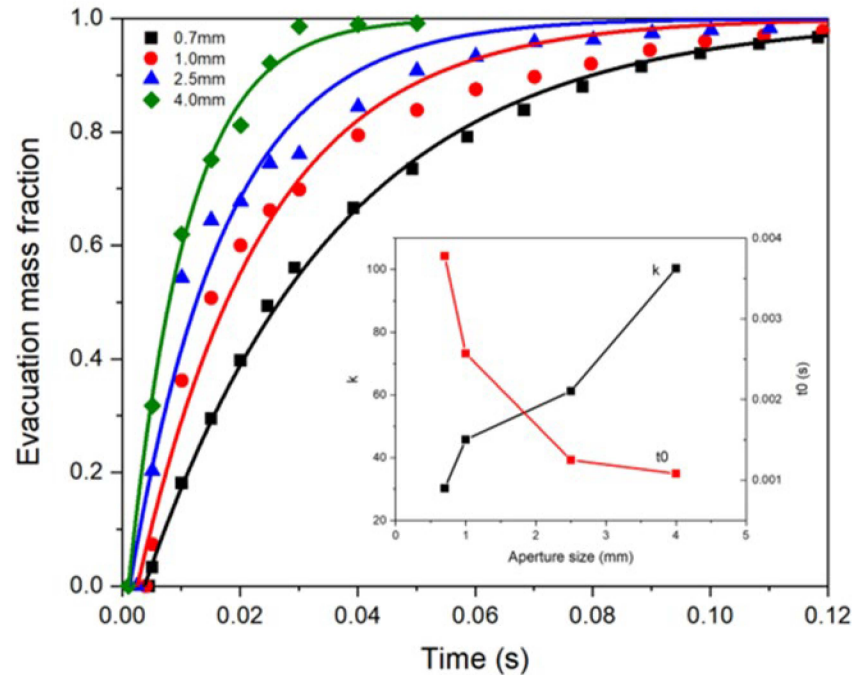
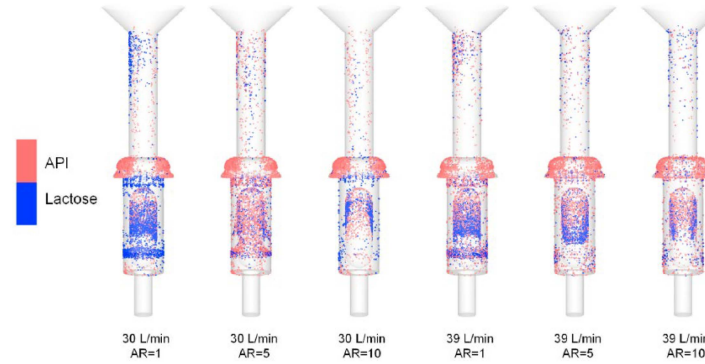
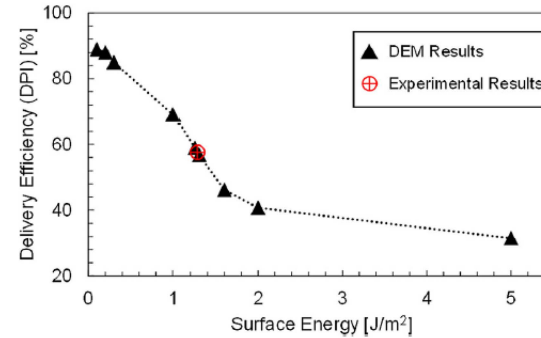
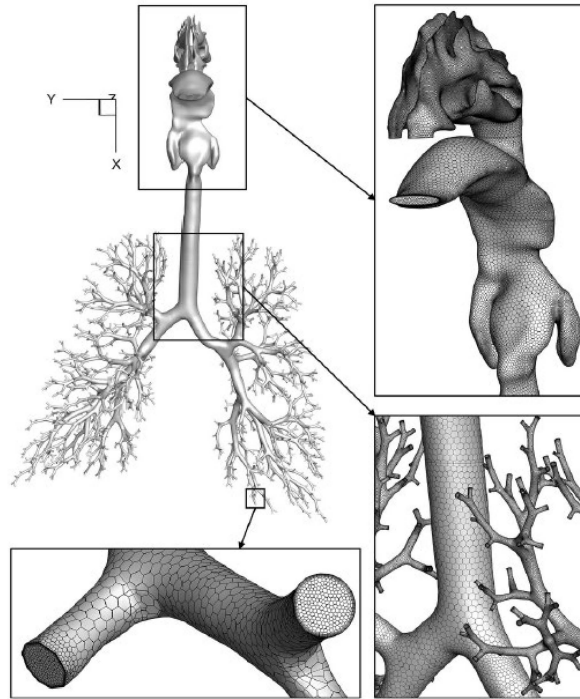
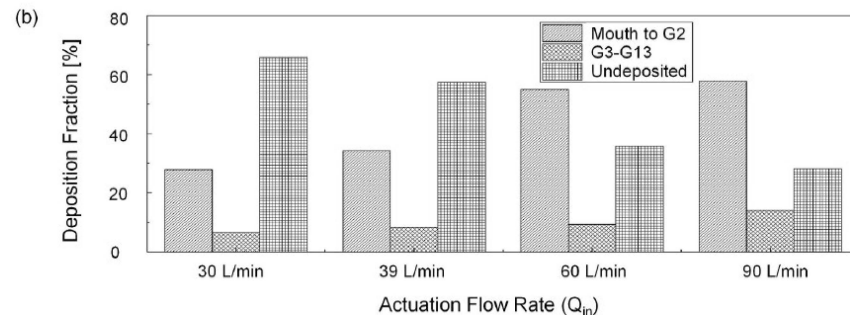
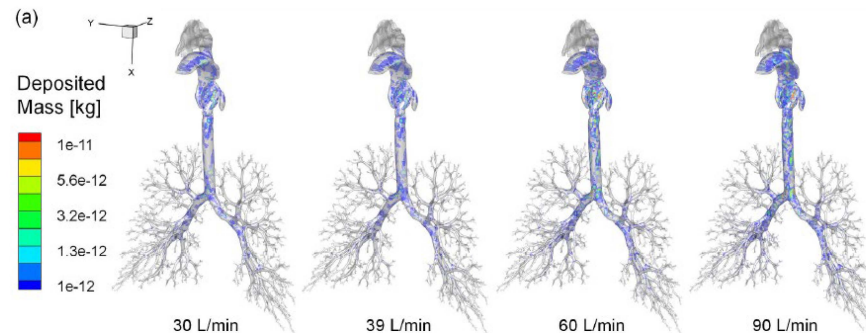
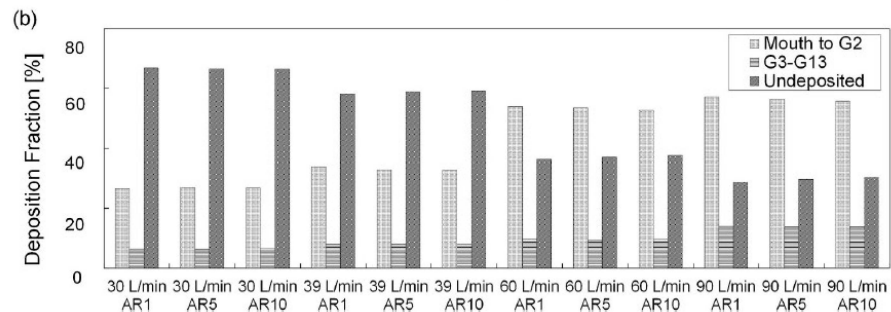
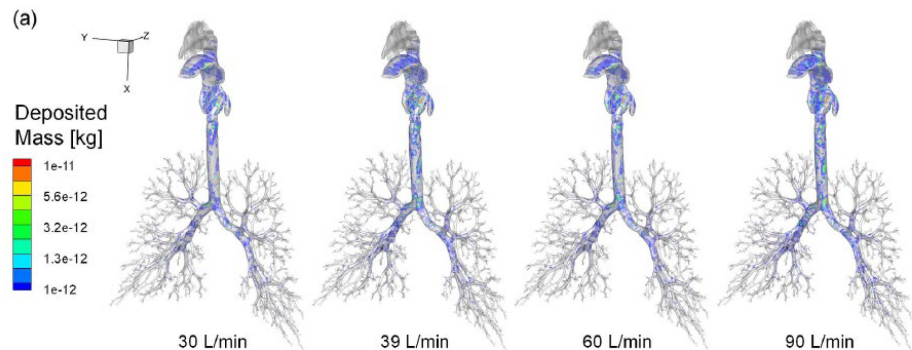


Figure 5. Particle evacuation from the capsule with time for various aperture sizes.

Effect of Carrier Particle Shape



Effect of Carrier Particle Shape



Effect of Device Geometry – Hypothetical Reservoir-Based DPI

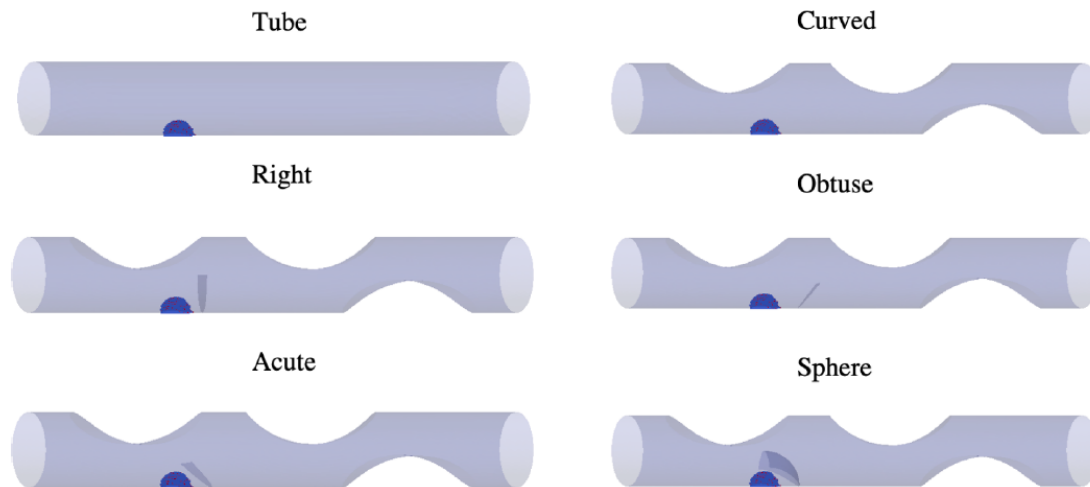


Fig. 8. Various device geometries are used to probe the relative importance of the interactions of the carrier particles with (i) the gas, (ii) other carrier particles, and (iii) the wall during inhalation. Each figure shows the settled pile of carrier and API particles, prepared in an identical fashion. (a) *Tube*: A simple cylindrical geometry; (b) *Curved*: A cylinder with wavy walls that would enhance the lateral motion of the gas and particles. (c) *Right*: Same device geometry as in case (b), except that a vertical baffle as shown in the figure is added to modify the flow. (d) *Obtuse*: Similar to case (c) except that the baffle is inclined towards the downstream direction. (e) *Acute*: Similar to case (d) except that the baffle is inclined towards the upstream direction. (f) *Sphere*: The baffle has the shape of a quarter of a sphere. The airflow is from left to right in all geometries.

Effect of Device Geometry – Hypothetical Reservoir-Based DPI

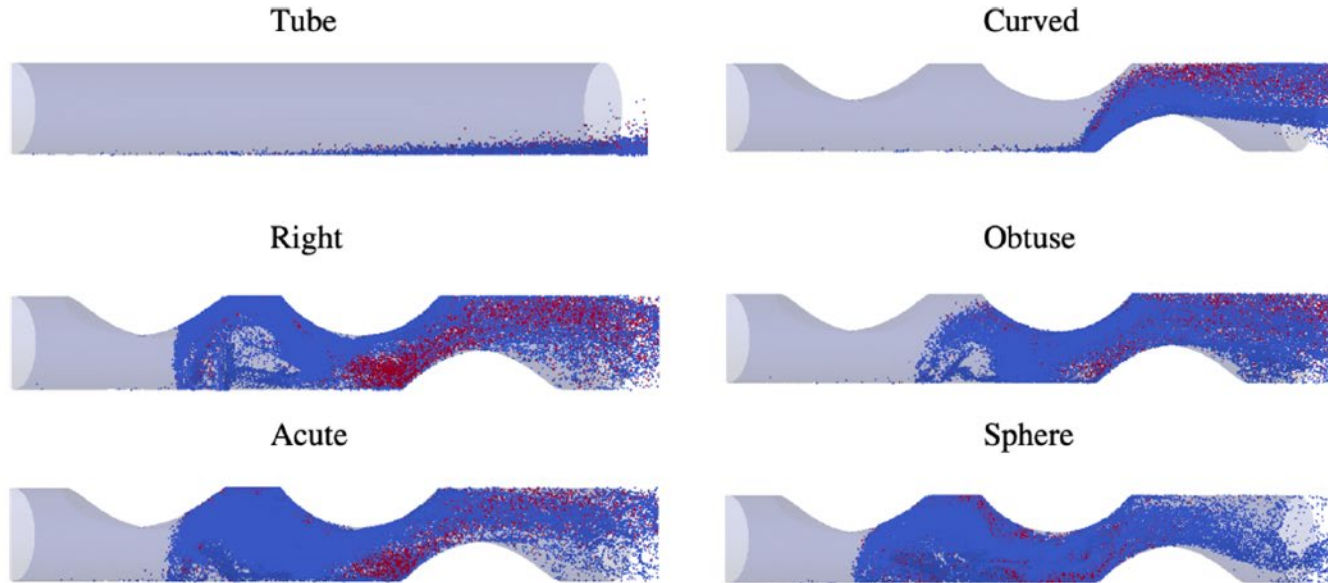


Fig. 13. Visualization of the carrier (blue) and API (red) particles at 0.0125s for the different device geometries. The maximum inhalation rate = 71 L/min.

Effect of Device Geometry – Hypothetical Reservoir-Based DPI

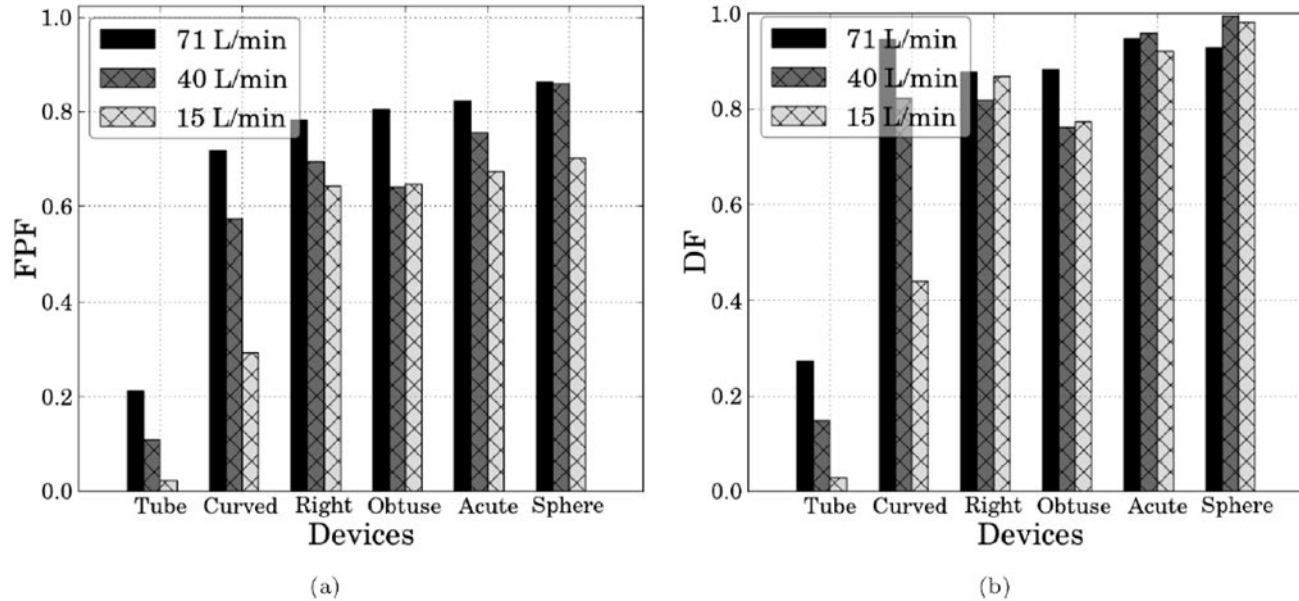


Fig. 10. The fine particle fraction (FPF) and dispersion fraction (DF) for different inhalation rates and different device geometries. The configuration of the pile is the same in all cases.

Anoro Ellipta – Umeclidinium Bromide and Vilanterol Trifenatate



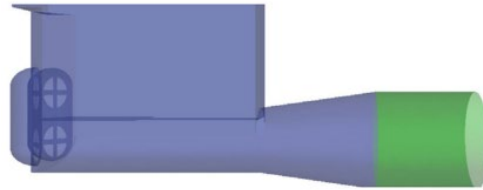
Blister #1

Umeclidinium bromide 62 mcg inhalation powder
Lactose monohydrate 12.5 mg carriers

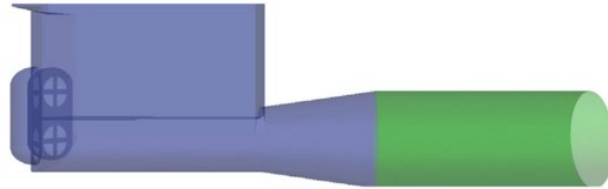
Blister #2

Vilanterol 25 mcg inhalation powder
Lactose monohydrate 12.5 mg carriers

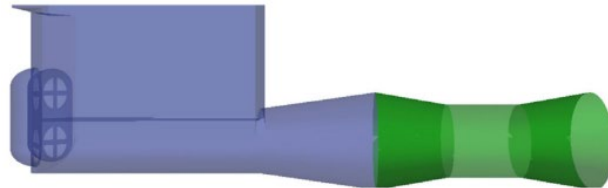
Effect of Device Modification



(a) Standard



(b) Extended

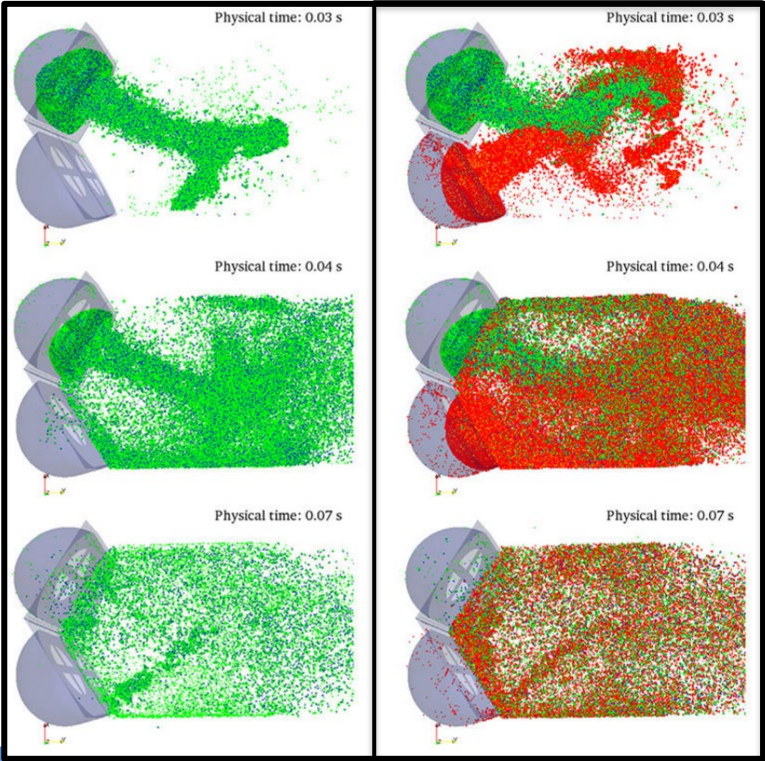


(c) Nozzle

Mouth-piece	FPF
Standard	38.7%
Extended	36.8%
Nozzle	43.1%

Effect of Second Blister

Would the presence of a second formulation affect the fine particle fraction (FPF)?



Case	FPF Left blister	FPF Right blister
Vilanterol – only single blister	38.7%	-
Vilanterol – in the presence of another blisters	60.8%	33.0%

The presence of a second formulation affects the FPF significantly.

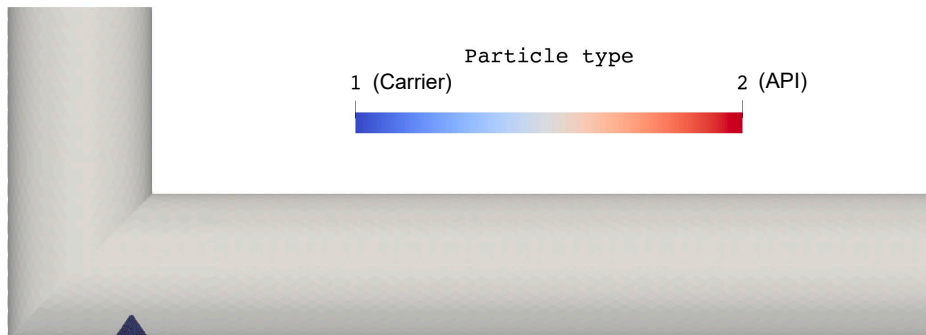
Figure 6 from Sulaiman et al.¹⁶

Experimentally Measured Particle Size Distribution (PSD)

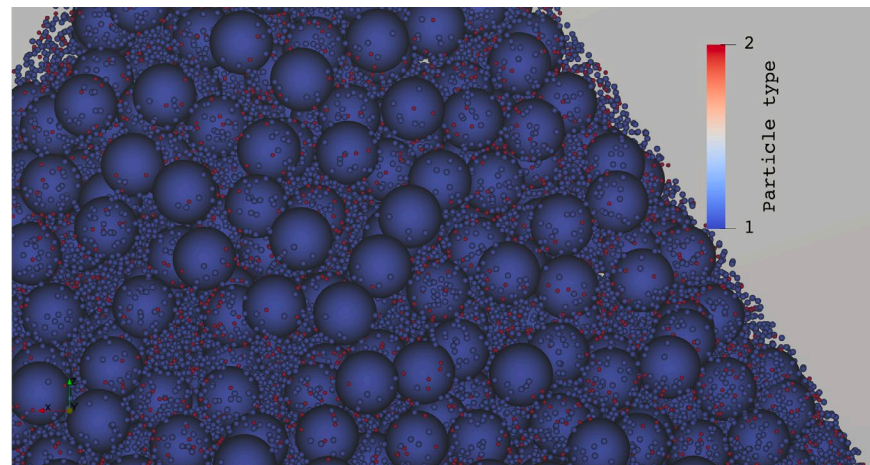
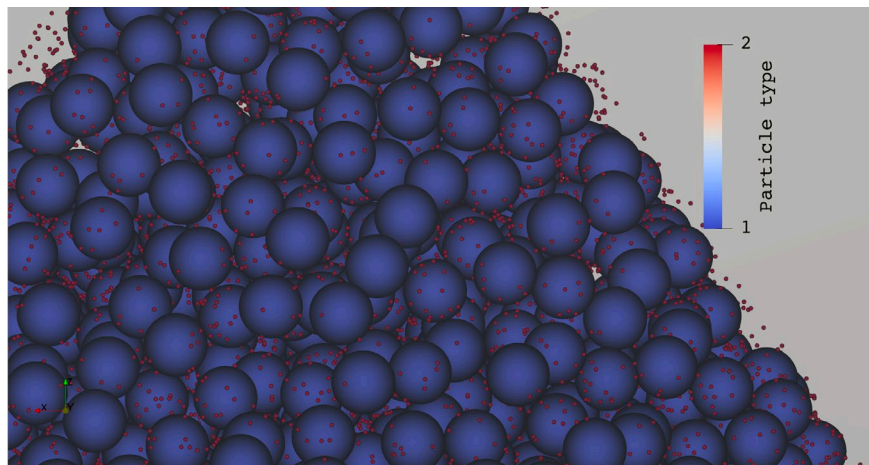


- Currently available DPI models use one representative size for both API and carrier particles (e.g., lactose monohydrate) and do not reflect the PSD data that are reported in new drug applications (NDAs), especially lactose fines.
- **Ongoing Internal Project**: Use CFD-DEM to gain insight on whether the effect of lactose fines needs to be considered in making modeling decisions.

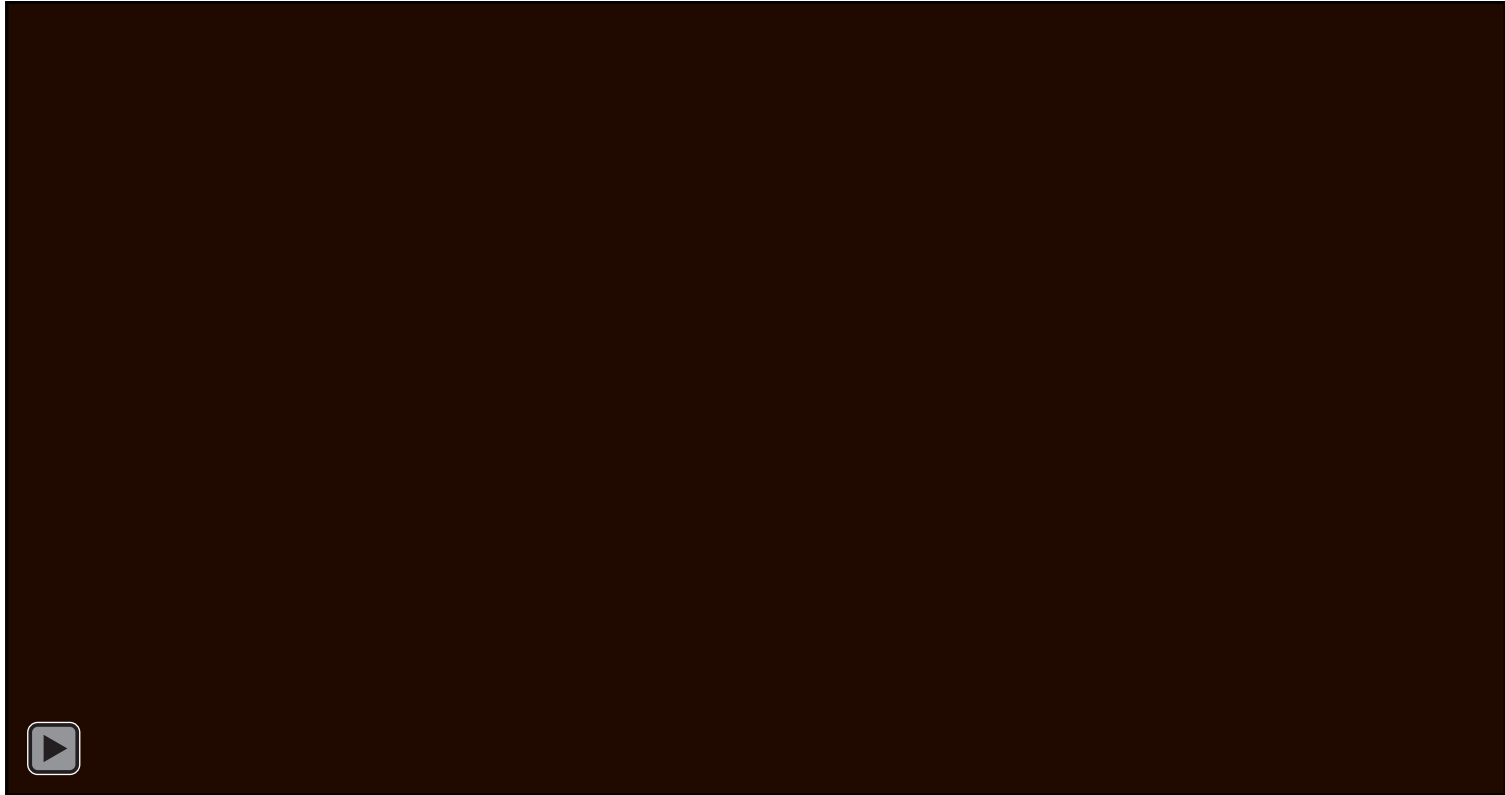
Effect of Lactose Fines



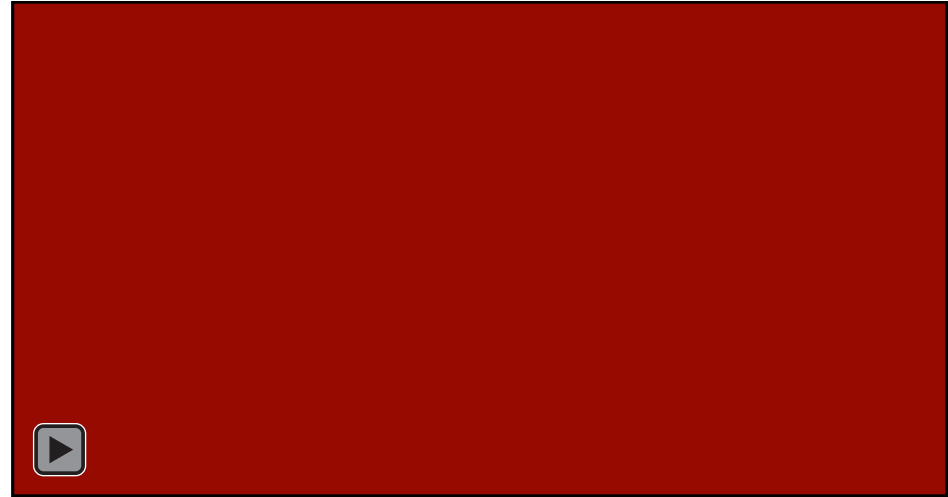
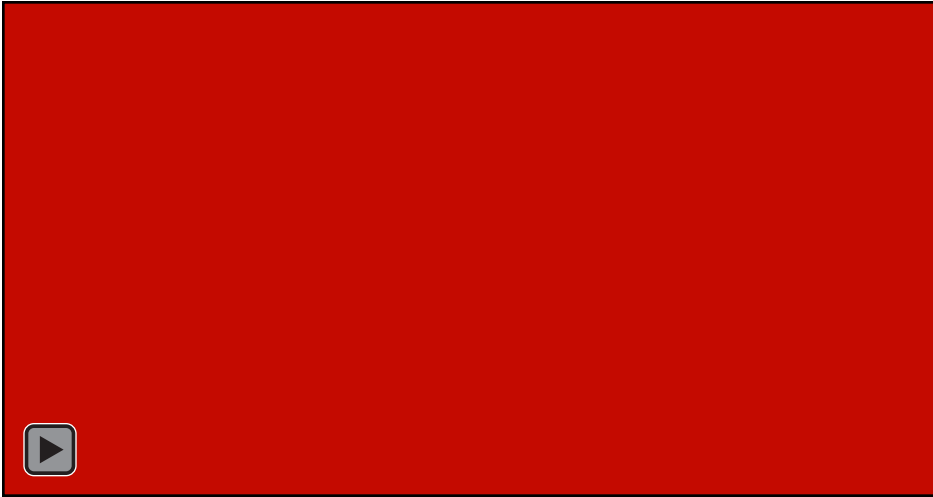
Model adapted from
Sulaiman et al.¹⁵



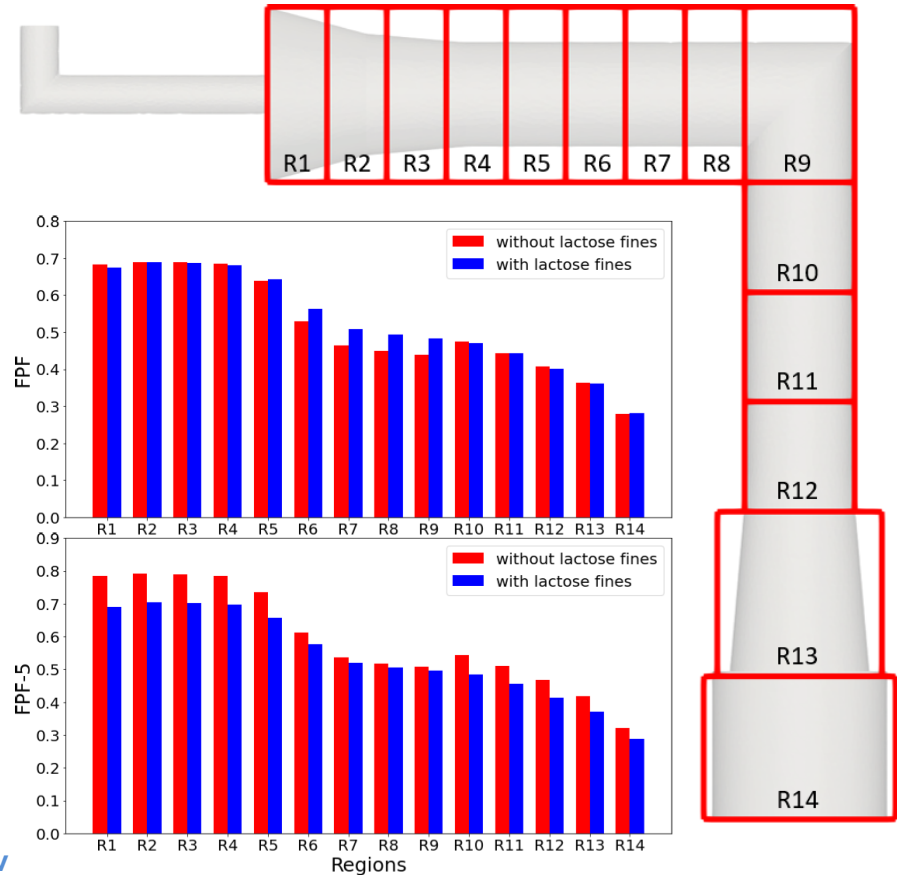
Effect of Lactose Fines



Effect of Lactose Fines

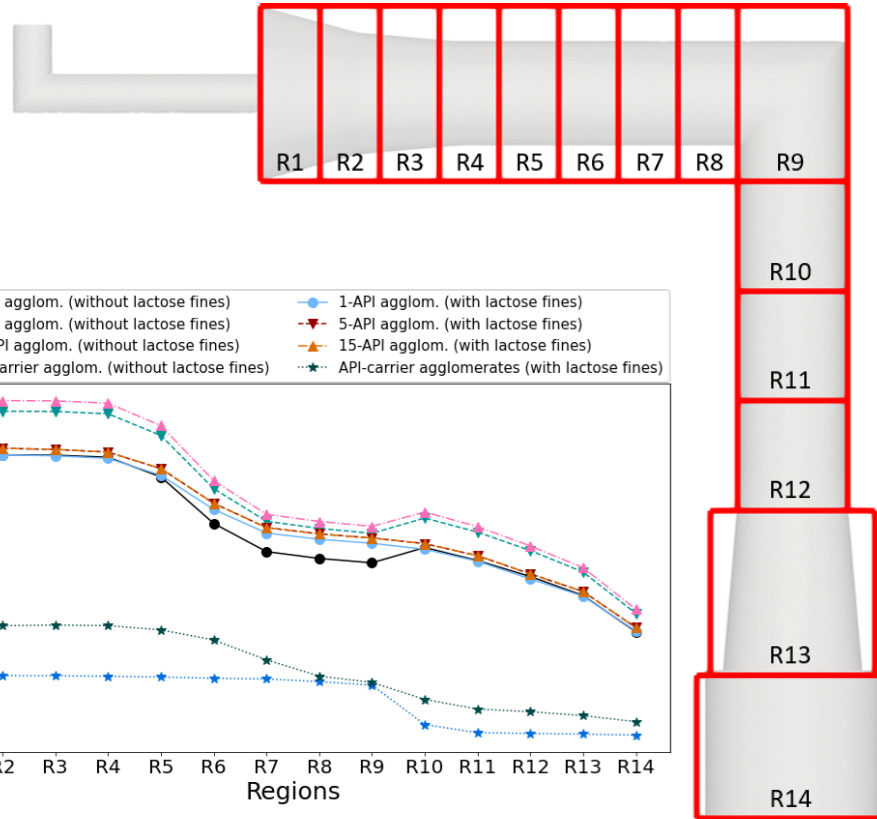


Effect of Lactose Fines



- Including lactose fines led to an increase in FPF in regions R5-R9, and a decrease in FPF-5 and FPF-15 in all regions.
- When the airflow bends down, the API particles agglomerated with large carrier particles are deagglomerated, but in the case with lactose fines, these API particles are potentially reagglomerated with lactose fines.

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Effect of Lactose Fines

- CFD-DEM results showed that lactose fines appear to help prevent formation of larger API agglomerates, but they also may increase the chance of API particles binding to the carrier particles.
- Although this difference may not be large in this study with this simple L-shaped device, it may have significant implications further downstream in the upper airway or in more complex DPI device geometries, such as those on the U.S. market that use a blister cap, capsule, or reservoir-based system.

Conclusion

- Coupled CFD-DEM is a powerful computational tool to simulate performance of DPIs by capturing particle-particle and particle-wall interactions including agglomeration and deagglomeration and fluid transport.
- CFD-DEM has potential to serve as a time- and cost-efficient strategy to accelerate product development and manufacturing involved in demonstrating bioequivalence of complex generic orally-inhaled drug products.
- Additional factors need to be considered if the model is an adequate representation and deemed credible for the context of use and the question of interest.

Conclusion

*“Everything should be made as simple as possible,
but not simpler”*

- Albert Einstein -

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