In Silico Study of the Effect of Including Lactose Fines in Modeling Dry Powder Inhaler Performance

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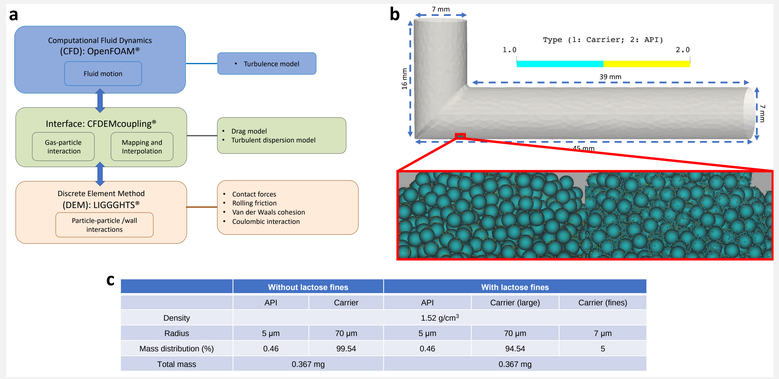
Purpose

Computational fluid dynamics (CFD) is a physics-based modeling approach used to simulate and predict fluid motion that serve as a time- and cost-efficient strategy to help demonstrate bioequivalence in the development of complex generic orally inhaled drug products. Many CFD models use a simplified point-mass approach to predicting particle transport, but discrete element method (DEM) is a popular alternative because it uses 3D volumetric representation of particles that can capture the forces between particles that influence agglomeration and deagglomeration. Modeling these interactions of particles with realistic sizes is crucial especially for dry powder inhaler (DPI) product performance to capture the interactions of carrier and active pharmaceutical ingredient (API) particles. A coupled computational fluid dynamics and discrete element method (CFD-DEM) model was used to simulate performance of a DPI that capture the particle-particle interactions and fluid transport in a realistic geometry. Currently available DPI models use one representative size for both API and carrier particles (e.g., lactose monohydrate) and do not reflect the particle size distribution (PSD) data that are reported in new drug applications (NDAs). In particular, these models do not incorporate lactose fines despite the importance of these particles for DPI performance.[1] The results from this study are expected to provide an in silico platform to gain insight on whether the effect of lactose fines needs to be considered in making modeling decisions.

Methods

Open-source packages were used to develop the CFD-DEM platform to simulate DPI actuation. OpenFOAM (OpenFOAM Foundation Ltd, London, UK) was used to perform CFD simulations, LIGGGHTS (DCS Computing GmbH, TECH HARBOR - Neue Werft, Austria) was used for particle simulations in DEM approach, and CFDEM (DCS Computing GmbH, TECH HARBOR - Neue Werft, Austria) was used to couple CFD and DEM to model the interactions between aerodynamics and particles. The model was previously developed by Princeton University for Grant 1U01FD006514[2] (see Figure 1a). A simple geometry was adopted from Sulaiman et al.[3] (Figure 1b) and added to the U.S. Pharmacopeia (USP) induction port to study the effect of adding lactose fine carrier particles into DPI simulations on agglomeration and deagglomeration of the API particles. The mesh was generated using ANSYS Fluent Meshing 2021 R2, resulting in 112,665 polyhedral cells and 327,248 prisms along the device surfaces.

The fluid phase was modeled by solving the volume-averaged equations of motion of the gas phase using a large eddy simulation (LES) approach with the dynamic Smagorinsky model, and the particle phase was modeled by solving Newton's equations of motion.[2,3] The particle-particle and particle-wall interactions are quantified by calculating the forces using a Hertzian spring-dashpot model.[4] A velocity inlet was uniformly applied at the inlet to prescribe a peak inspiratory flow rate of 71 L/min.



c

	Without lactose fines		With lactose fines		
	API	Carrier	API	Carrier (large)	Carrier (fines)
Density	1.52 g/cm^3				
Radius	5 μm	70 μm	5 μm	70 μm	7 μm
Mass distribution (%)	0.46	99.54	0.46	94.54	5
Total mass	0.367 mg		0.367 mg		

Figure 1. a. An open-source platform for CFD-DEM simulations originally developed by Princeton University as part of a grant funded by the Office of Generic Drugs in 2014 (1U01FD006514). **b.** The geometry from Sulaiman et al.[3] that was used in the simulations. The red box shows two cases tested in this study: without (*left*) and with (*right*) lactose fines. **c.** Particle parameters used in the DEM simulations.

Results

A fully-coupled fluid-particle simulation of was performed (Figure 2a) to compare the performance of a DPI with or without lactose fines (Figure 2b). High dispersion and mixing of particles due to turbulence flow are observed. To quantify the agglomeration and deagglomeration of the API and carrier particles, we calculate the fine particle fraction (FPF), which is defined as

$$\mathbf{FPF} \equiv \frac{\text{weight of API fragments}}{\text{total weight of API particles at time zero}}$$

The USP induction port is segmented into 14 different regions (Figure 3a), and FPF is measured in each of those regions. In each region, FPF for single-API fragments (FPF; Figure 3b), fragments consisting of 5 or less API particles (FPF-5; Figure 3c), and fragments consisting of 15 or less API particles (FPF-15; Figure 3d). Figure 3b-3d show that 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. This suggests that without lactose fines, the API particles form larger agglomerates. One interesting observation is that for the case without lactose fines, FPF, FPF-5, FPF-15 all increase from R9 to R10. To better understand the observation, we look at the number of API-API and API-carrier agglomerates in each region (Figure 4). It is evident in Figure 4 that for the case without lactose fines, there is a larger decrease in the number of API-carrier agglomerates from R9 to R10 and an increase in the number of API-API agglomerates. In comparison, with the addition of lactose fines, the decrease in the API-carrier agglomerates is not as dramatic, and the number of API-API agglomerates continues to decrease. This suggests that between R9 and R10, the API particles agglomerated with large carrier particles are deagglomerated, but in the case with lactose fines, these API particles are potentially reagglomerated with these lactose fines. Figure 4 also shows that the number of API-API agglomerates with 5 or less API particles and that with 15 or less API particles is the same, which suggests that lactose fines may prevent the formation of large API-API agglomerates.

Results Cont.

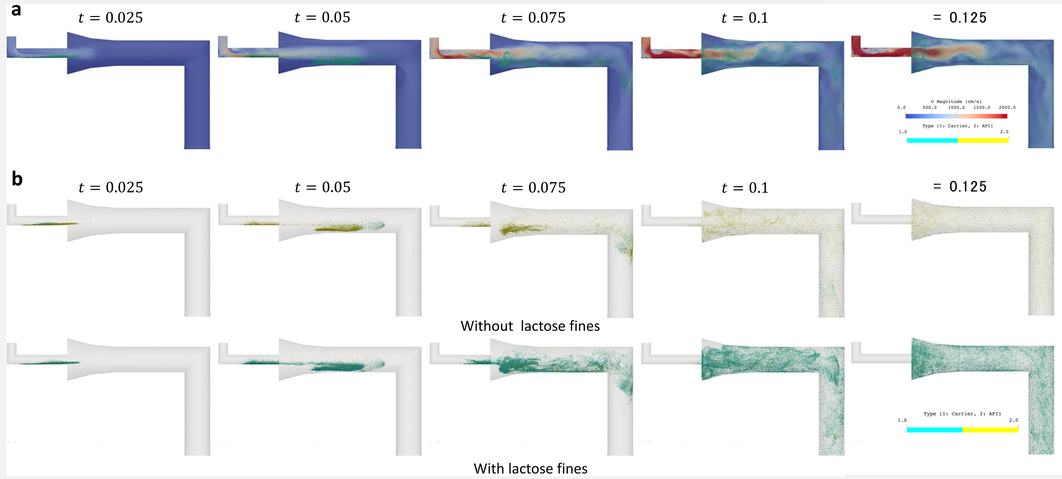


Figure 2. a. A fully-coupled fluid-particle simulation of the DPI performance using a simple geometry from Sulaiman et al.[3] The blue-red color scheme represents the fluid velocity magnitude (cm/s), and cyan-yellow color scheme represents different types of particles. **b.** A comparison of CFD-DEM simulations of a DPI in a simple geometry to study the effect of lactose fines. Top panels show a simulation with just the API (yellow fine particles) and large lactose (cyan spheres) particles. Bottom panels show a simulation additionally including lactose fines (cyan fine particles).

Note: The particle sizes are rescaled to improve the visibility of the API particles.

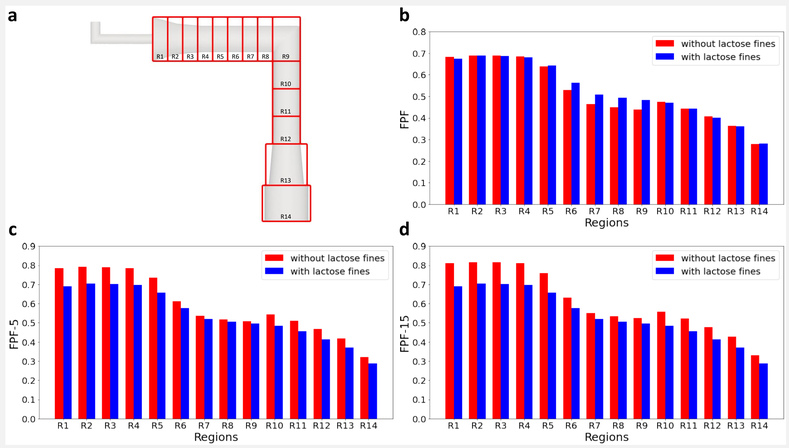


Figure 3. a. Measurement regions in the USP induction port, in which fine particle fraction (FPF) for fragments consist of **b.** one API particle, **c.** five or less API particles, and **d.** 15 or less API particles.

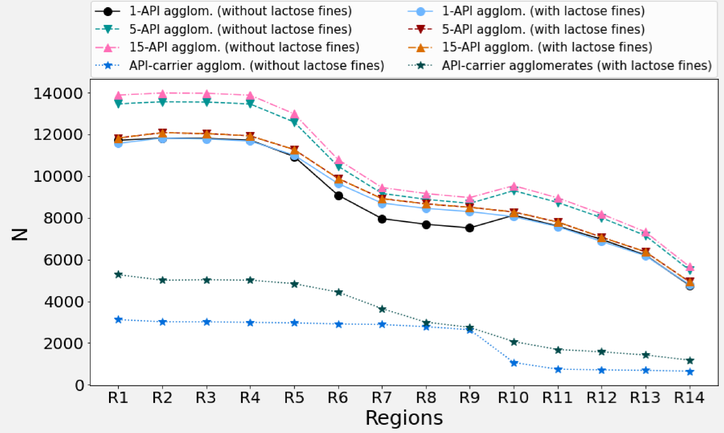


Figure 4. The number of API-API and API-carrier agglomerates that pass through each region shown in Figure 3a.

Conclusions

A CFD-DEM model was developed to study the effect of lactose fines in a simulation of DPI performance. Simulation results showed that there is an apparent difference in the way API particles and lactose carrier particles interact with/without the presence of lactose fines. 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.

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