

# **DEM-CFD Simulation of Fluid-Particle Flow in Carrier-Based Dry Powder Inhalers for Pharmaceutical Applications**

PhD Thesis Extended Abstract

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## Summary

The research investigates the complex dynamics of multiphase flow and aerodynamic dispersion in Dry Powder Inhalers (DPI) used for the treatment of respiratory diseases such as asthma and Chronic Obstructive Pulmonary Disease (COPD). DPI are medical devices for inhalation that do not require propellants; instead, the patient's own inhalation generates an airflow that passes through a complex geometry of curves, obstacles, and flow restrictions designed to induce a cyclonic motion. This airflow enables the dispersion of the powdered drug, allowing it to reach the patient's airways.

The focus is on carrier-based formulations, in which the fine Active Pharmaceutical Ingredient (API) is blended with a coarse excipient to enhance flowability and handling. Upon reaching the upper airways, the API must detach from the carrier so that the excipient is retained in the throat while the API continues its path into the lower respiratory tract. The objective is to deeply understand the mechanisms governing API delivery to improve DPI efficiency.

Modelling such devices requires the coupling of phenomena occurring at different levels: the device scale, the carrier particle scale, and the API particle scale. Computational Fluid Dynamics (CFD) and Discrete Element Method (DEM) simulations are employed to model and analyse the interactions between airflow and particles at multiple scales.

The multiscale modelling approach is developed with increasing complexity, both in terms of modelling and numerical methods, while considering two different device geometries. The air-particle fluid dynamics is analysed by incorporating the key mechanisms responsible for the dispersion of carrier particles, coated carrier particles, and the detachment of the active pharmaceutical ingredient.

Models for each of these mechanisms are implemented and validated within the CFD-DEM framework. The study progressively refines these models, with each stage building upon the findings of previous analyses. The results provide critical insights into API release and DPI performance, contributing to the development of more efficient inhalers and improved drug delivery.

## Problem addressed

Despite the widespread use of DPI in respiratory drug delivery, their efficiency remains relatively low, with only 20% to 40% of the drug reaching the lungs [1]. Carrier-based formulations improve powder flowability, but the deaggregation process—where the API detaches from the carrier—is not yet fully understood. The microscopic interactions between API and carrier particles are difficult to capture experimentally due to the limitations of macroscopic observational techniques. Understanding these mechanisms is crucial for optimizing inhaler performance and ensuring effective drug delivery, as well as for designing inhalers with increasingly efficient geometries and advanced features that enable the effective delivery of different formulations. To support the development of more efficient and effective devices, numerical simulation tools can serve as valuable allies, as they allow for the accurate reproduction of local air-particle flow dynamics.

## State of the Art

Several studies have attempted to analyse DPI efficiency through experimental and computational approaches. Conventional experimental methods, such as laser diffraction [2], image analysis [3] and impaction measurements [4], provide valuable macroscopic data but fail to capture particle-scale interactions. Computational models, particularly CFD and DEM, have emerged as powerful tools for simulating fluid-particle interactions in DPI [5-8]. However, previous numerical studies have faced challenges in accurately representing cohesive forces, carrier-wall interactions, and the interplay between fluid flow, carrier and API particles.

This study builds on existing research by developing a comprehensive CFD-DEM framework that incorporates the explicit simulation of both carrier and API particles, detailed carrier-API interactions, and a broader range of influencing factors.

## Key Scientific and Technological Innovations

- **First-of-Its-Kind Simulation**

According to Capececiaturo et al. [9], this is the first study to simultaneously simulate both carrier and API particles alongside the fluid phase, providing an unprecedented, realistic representation of DPI dynamics.

- **Smart Multiscale Modelling**

A tailored selection of physical models (polydisperse drag, lift forces, rolling friction, cohesion/adhesion) has been implemented to capture the critical mechanisms of DPI performance, optimizing model accuracy with reasonable complexity.

- **Optimized CFD-DEM Coupling**

A systematic evaluation of coupling strategies has identified the most efficient and accurate method to simulate air-particle interactions, setting a new benchmark for DPI computational modelling.

- **Understanding Airflow and Cyclonic Motion**

The research provides new insights into how DPI geometries create airflow resistance and induce cyclonic motion, improving inhaler designs and optimizing drug dispersion.

- **Tracking Individual Particle Trajectories**

A detailed particle trajectory analysis correlates drug dosage, initial position, formulation type, and patient airflow, offering key insights into drug delivery efficiency.

- **Mechanistic API Detachment Model**

A physics-based model replaces traditional empirical approaches, delivering more accurate predictions of API detachment and enhancing DPI formulation strategies.

- **Comparison of First- and Next-Generation DPI Designs**

A direct comparison between first-generation capsule-based DPI and next-generation reservoir devices reveals why older models often outperform newer ones, highlighting crucial design factors that influence drug dispersion.

- **Stepwise Model Validation**

A progressive validation strategy ensures that each modelling refinement is backed by experimental or theoretical validation, enhancing reliability and real-world applicability.

## Applications

- **Pharmaceutical Industry**

The findings contribute to the optimization of DPI designs, leading to improved drug delivery efficiency and reduced medication waste.

- **Computational Modelling**

The validated CFD-DEM framework serves as a foundation for future research, allowing more accurate predictions of DPI performance.

- **Powder Technology**

The methodology is applicable to various fields, including powder processing, aerosol engineering, and controlled-release formulations.

# Implementations and results

## Development of simulation tool

The Computational Fluid Dynamics - Discrete Element Method (CFD-DEM) is a powerful simulation technique for modelling fluid-particle interactions in multiphase systems. It combines CFD to solve the fluid phase (Navier-Stokes equations) and DEM to track individual particles, capturing key phenomena such as drag, adhesion, cohesion, and friction.

A two-way coupling approach is used: the fluid influences particle motion, while particles, in turn, alter the fluid flow, ensuring an accurate representation of real-world dynamics. Advanced physical models have been integrated into open-source CFD-DEM frameworks (MFiX and OpenFOAM) to account for the most relevant mechanisms, alongside code optimizations and post-processing tools (in MATLAB and Paraview) for improved computational efficiency and detailed analysis.

Furthermore, an in-house design of a swirl-based DPI (Figure 1) has been developed to represent key features of next-generation inhalers, ensuring that the simulation tool can capture the critical aspects of modern DPI performance. The following elements have been included: a hemi-spherical dose cup at the base of the system that houses the initial dose of drug product, a swirl chamber with two symmetrical tangential inlets and two eccentric hemi-circular walls between which the air flow develops, and a cylindrical exit duct on top of it. The air flow is supposed to generate a vortex in the swirl chamber, whose central low-pressure region, aligned with the dose cup, is responsible for the initial particle suction from the cup. The designed geometry is integrated into the CFD-DEM framework to analyse and optimize powder dispersion and drug delivery within realistic device conditions.

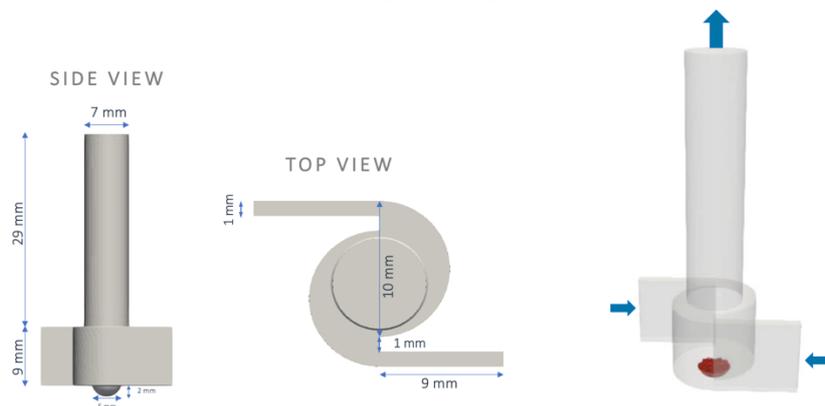


Figure 1 In-house designed DPI. Side view, top view and 3D transparent representation. In the last one, blue arrows denote the two air inlets and the air outlet from the top of the exit duct; the red part represents the particles filling the hemispherical dose cup.

## Air flow and carrier motion

CFD-DEM simulations have been conducted to analyse fluid flow and carrier particle motion, focusing on powder emission dynamics, particle trajectories, and velocity fields. The airflow exhibits a cyclonic and vortical motion (Figure 2a), which plays a crucial role in particle dispersion and inhaler efficiency. The study has identified three distinct stages of powder release which are correlated with different types of characteristic particle trajectories (Figure 2b).

A parametric analysis has been performed to determine the key factors influencing inhaler efficiency and powder dispersion, including particle size, inhaler geometry, and particle mechanical properties. Results have highlighted the importance of choosing appropriate physical models to accurately capture carrier dynamics and drug delivery performance.

The study reveals that carrier-wall adhesion influences powder release, with some particles sticking to the inhaler walls, and that a high number of high-velocity collisions occur in the swirl chamber, suggesting that API release may begin within the inhaler itself.

The coupling approach is found to be critical in describing particle-fluid interactions. The commonly used one-way coupling method in the literature oversimplifies the phenomenon, failing to capture key

dynamics. In contrast, a two-way coupling approach provides a more accurate representation of carrier motion and powder dispersion (Figure 2c).

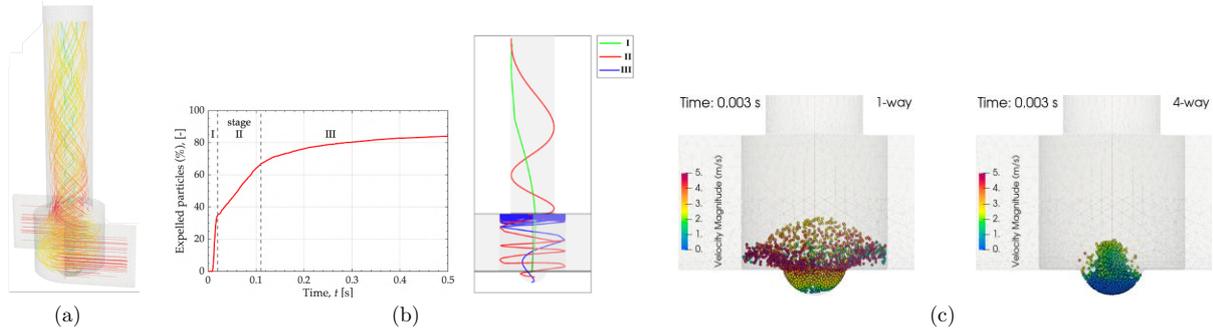


Figure 2 a) Streamlines of fluid flow, coloured according to gas velocity. b) Powder emission stages and corresponding characteristic particle trajectories. c) Carrier particles lifted from the cup in simulation with 1-way coupling approach (left, unrealistic) and 4-way coupling (right, realistic).

Another major factor affecting the results is the inlet flow rate profile. While many studies assume a constant stepwise flow rate, simulations using a realistic, time-dependent profile based on actual patient data yield significantly different results. The transient initial phase, which always occurs in real inhalation, slows down the process considerably, preventing proper powder dispersion and deaggregation (i.e., API release from the carrier). A stepwise flow rate proves to be much more effective. The results highlight the importance of mechanical devices that ensure the powder is directly exposed to a fully developed airflow, optimizing drug delivery and inhaler performance. Such mechanical mechanisms are often integrated into next-generation multidose inhalers, further enhancing their efficiency.

Experimental validation has been conducted using data from an inhaler similar to the one designed in-house, ensuring the reliability of the numerical models. The simulations successfully replicate the initial emission peak of the drug but highlight discrepancies in capturing long-term dispersion behaviour, indicating areas for further refinement (Figure 3).

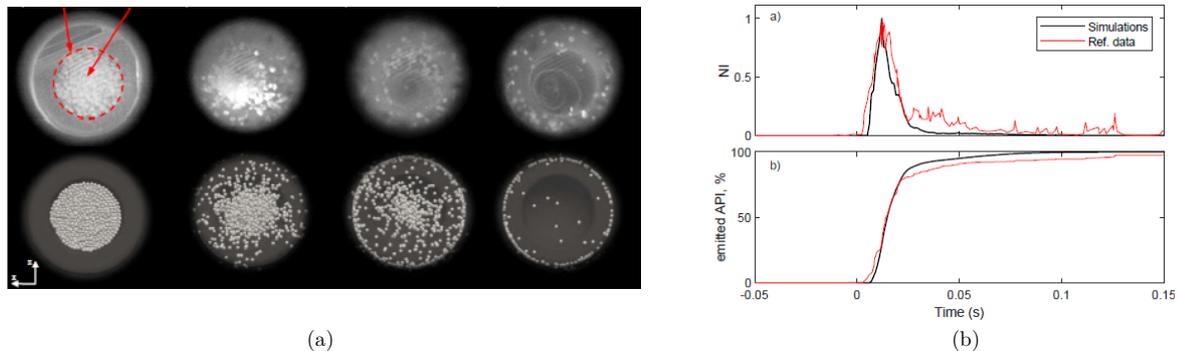


Figure 3 Comparison of CFD-DEM simulation with experimental data available in literature [3]. a) Cup emptying, top view. Experimental data (top) and simulation results (bottom). b) Drug emission from the inhaler in simulations and experiments. Normalized instantaneous flowrate (top), cumulative percentage (bottom).

### API deaggregation studies

API particles are introduced in the simulations by considering a single API particle attached to a carrier (Figure 4). This simple, fundamental system provides insights into deaggregation due to carrier-wall collisions. The concept of escape velocity, defined as the carrier-wall impact velocity above which API release occurs, is introduced. An analytical model for escape velocity is proposed and validated through DEM simulations.

The influence of cohesion energy, simulation timestep, restitution coefficient, and friction on escape velocity is investigated. Detachment becomes more difficult as the granular Bond number (i.e., API-carrier adhesive forces) increases. A larger timestep slightly facilitates detachment by reducing the

accuracy of impact description in the simulation. An increase in escape velocity is observed with higher static friction or a lower restitution coefficient, highlighting the significant role of powder mechanical properties. The effect of rolling friction is further analysed by examining the velocity, angular velocity, and overlap profiles of both API and carrier during carrier-wall impact. Without rolling friction, the API particle (if not detached) orbits indefinitely around the carrier. The inclusion of rolling friction dampens this motion, limiting angular velocity increase and stabilising the fine particle.

Finally, calculated escape velocity values are compared to typical carrier-wall impact velocities reported in the literature, suggesting that a single carrier-wall collision might lead to almost complete deaggregation, although some particles are likely to remain attached.

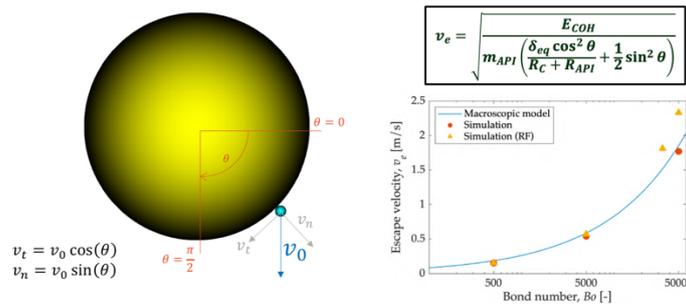


Figure 4 Schematic configuration considered for the evaluation of the escape velocity (left), analytical model (top, right) and results of the analytical model compared to DEM simulation as a function of granular Bond number (bottom, left).

## Simulation of Carrier-API Formulations

A custom algorithm has been developed to generate carrier particle configurations coated with API at a prescribed dosage (Figure 5a), allowing the explicit simulation of a two-component system consisting of 10 mg of 200-micron carrier particles coated with 10-micron API particles (Figure 5b). DEM allows tracking of all API particles during their initial lift-off, some still attached to the carrier particles, others already deaggregated. The particle-scale force balance provides valuable information on the complex interplay between adhesion/cohesion and hydrodynamics.

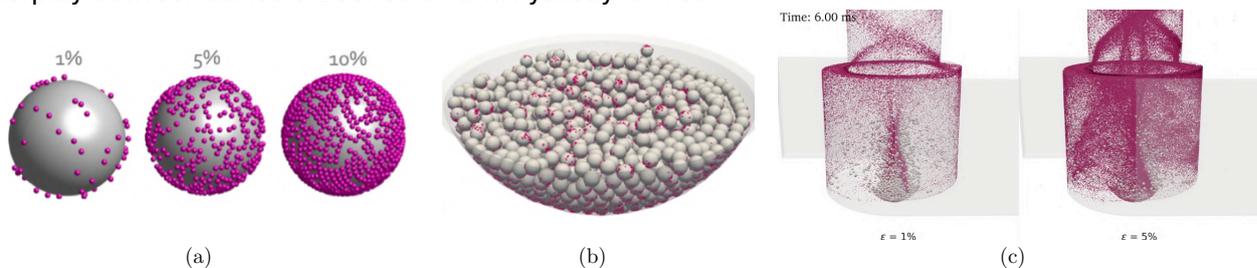


Figure 5 a) Generation of the coated carrier particles by random positioning of API particles (purple) on carrier particles (grey) for different weight dosages (w/w). b) Initial configuration of 1585 coated carrier particles with 1% API. c) Position of particles in the simulations with 1% and 5% weight dosage.

The effect of flow rate profile, cohesion model, weight dosage, and drag model has also been investigated. An increasing flow rate promotes faster emission and deaggregation of the active ingredient, while a higher API dosage (5%) shows that the deaggregation process of the API from the carrier may be limited by a high fines concentration (Figure 5c). The cohesion model plays a role as well, as the deaggregation process appears unrealistically easy when a simplified cohesion model is considered.

The study establishes that complete simulation of API-carrier systems with a 1:20 size ratio is computationally feasible despite three inherent challenges: (1) necessary particle loading restrictions, (2) nanosecond-scale timesteps (typically 1-10 ns) to resolve micron-sized API dynamics, and (3) extensive contact detection overhead. The successful simulations capture all critical phenomena -

including particle-fluid interactions, interparticle collisions, and wall impacts - while maintaining numerical stability.

### Capsule-Based DPI

During an abroad research period at the University of Magdeburg under the supervision of Prof. Martin Sommerfeld, OpenFOAM has been employed to conduct advanced computational fluid dynamics (CFD) simulations. The study focuses on the Cyclohaler, a commercially available DPI widely used for multiple drug formulations. This single-use capsule device requires capsule replacement for each inhalation, making its powder dispersion mechanics particularly dependent on capsule-inhaler interactions during operation.

Turbulence has been modelled using Large Eddy Simulation (LES), which provides a highly resolved representation of gas flow fields (Figure 6a). A comparative analysis between LES and Reynolds-Averaged Navier-Stokes (RANS) methods demonstrates that LES delivers superior accuracy, as it explicitly resolves large vortex structures while modelling only the smallest scales.

Furthermore, Discrete Element Method (DEM) simulations are performed to investigate capsule rotation and vibration, offering insights into carrier particle release and active pharmaceutical ingredient (API) deaggregation (Figure 6b). The results reveal that capsule-inhaler collisions play a critical role in API release, significantly affecting the degree of API coverage on the carrier. Notably, this mechanistic insight could explain why first-generation capsule-based DPI, like the Cyclohaler, often outperform newer multi-dose reservoir devices: the vigorous capsule motion enhances powder fluidisation and deaggregation, whereas static reservoir systems may lack equivalent energy input. These findings highlight the importance of capsule dynamics in DPI performance, advancing the understanding of powder dispersion mechanisms in the Cyclohaler and providing a potential rationale for the observed efficacy of older devices.

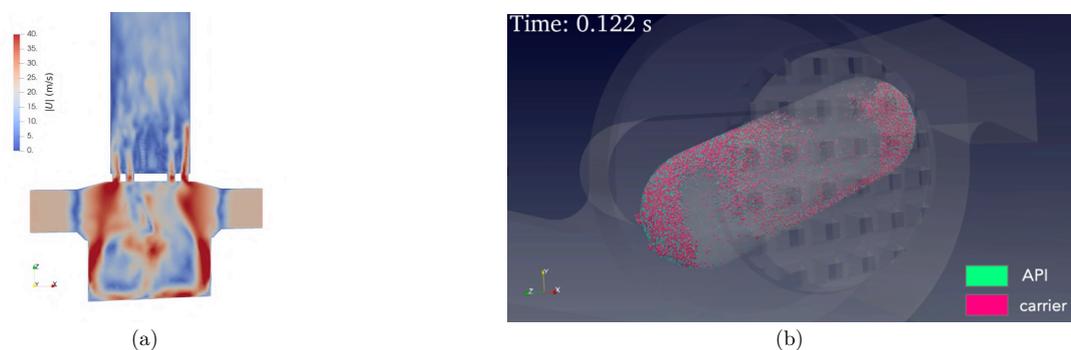


Figure 6 Simulations of the capsule-based DPI Cyclohaler. a) Fluid flow modelled with LES turbulence, b) DEM simulation of particle motion inside the capsule.

### High-Dose Formulation Challenges

In the final part of the study, the focus is on evaluating the release dynamics of a high-dose carrier-based system in the swirl-based in-house designed DPI. As DPI often fail to provide good performance with high-dosage formulations, the objective is to identify potential inefficiency factors.

The diameter of API particles is even smaller than in the previous case, set at 5 microns, which is a more realistic size for active pharmaceutical ingredients. Additionally, budesonide, a commonly used API in inhalation formulations, is chosen as a reference model, with its properties carefully selected in the simulations to ensure an accurate representation. The carrier-API formulation considered is lactose (carrier) – budesonide (API), characterised by API-API cohesion (250 nN) being higher than API-carrier adhesion (65 nN). To maintain the computational load manageable, only a selected number of carrier particles (from 1 to 4) are coated with multiple layers of 5-micron API particles, reaching weight dosages of 5% and 10% (relative to the individual coated carrier particle). In this case, the size ratio is 1:40. The resulting configurations are shown in Figure 7a.

This system is then used to analyse new, more advanced CFD-DEM models, particularly the use of a drag model specific to polydisperse systems, the introduction of lift forces (Saffman and Magnus), and fluid torque. All these models have been implemented in the in-house version of the code. The results show that initial deaggregation is overestimated with the standard Gidaspow drag model, while the use of polydisperse drag models allows a more accurate estimate of the drag force acting on API particles. Lift forces influence carrier motion, and rotation is overestimated without fluid torque.

Subsequently, the effect of the initial position of the coated particle is evaluated, revealing an influence on both trajectories and timing. The impact of dosage is also assessed by comparing the results obtained with 5% and 10% dosage. It is observed that a locally higher amount of fine particles leads to the formation of large API clusters (Figure 7b) and an increased probability of re-agglomeration, likely causing reduced inhaler efficiency.

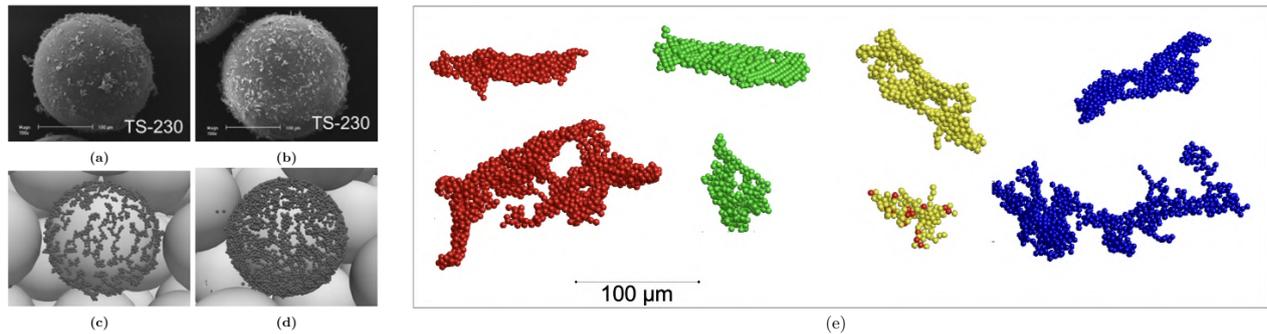


Figure 7 Scanning electron microscopy images of (a) low (carrier:drug=85:1) and (b) high (carrier:drug=5:1) dosage carrier-drug blends with a 230 µm spherical carrier particle [10] compared to configuration used in the simulations: c) lower dosage (5%), d) higher dosage (10%). e) Examples of detached API clusters observed in the CFD-DEM simulations with higher dosage (10%).

Finally, the deaggregation phenomena of the salbutamol-lactose system, characterised by high API-carrier adhesion forces (180 nN) and low API-API cohesion forces (11 nN), is investigated in the same DPI. The results are presented in terms of Fine Particle Fraction (FPF), defined as the fraction of the total emitted dose consisting of particles or clusters below 5 microns in aerodynamic diameter, which are considered capable of reaching the deep lung.

The different cohesive properties ultimately result in a greater FPF (Figure 8a), but also in a higher percentage of particles delivered still adhered to the carrier (Figure 8b). The dispersion phenomenon is therefore strongly dependent on the formulation, suggesting that different inhaler geometries may be necessary for different drug-carrier combinations.

The study demonstrates the feasibility of tracking the local evolution of governing phenomena and particle motion, offering valuable qualitative information for optimised DPI design. Overall, CFD-DEM simulations prove to be a powerful tool for linking the micro-scale and macro-scale characteristics of aerosolization and dispersion processes in dry powder inhalers.

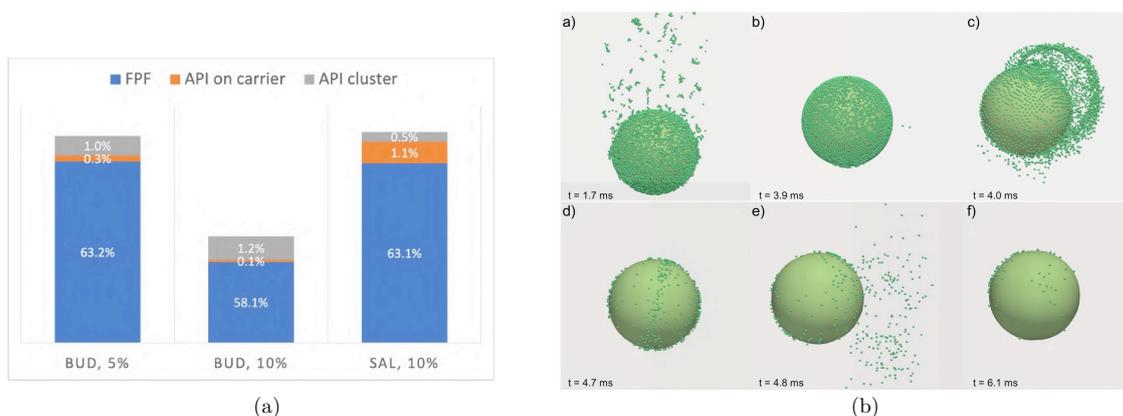


Figure 8 a) State of the API particles emitted from the inhaler in the first 20 ms for the three simulations considered: budesonide (BUD), 5% dosage; budesonide, 10% dosage; salbutamol (SAL), 10% dosage. b) Deaggregation stages of API particles in the salbutamol-lactose system.

## Conclusion

The research underscores the importance of full-scale DEM simulations in analysing deaggregation mechanisms and optimizing DPI performance. The developed numerical framework offers both qualitative and quantitative insights into fluid-particle interactions, serving as a valuable tool for enhancing inhaler design and drug formulation. Future work should focus on refining turbulence models, incorporating more complex particle interactions, and validating findings through additional experimental comparisons.

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