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Wall collision and drug-carrier detachment in dry powder inhalers: Using DEM to devise a sub-scale model for CFD calculations

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ABSTRACT

In this work, the Discrete Element Method (DEM) is used to simulate the dispersion process of Active Pharmaceutical Ingredients (API) after a wall collision in dry powders inhaler used for lung delivery. Any fluid dynamic effects are neglected in this analysis at the moment. A three-dimensional model is implemented with one carrier particle (diameter 100 μm) and 882 drug particles (diameter 5 μm). The effect of the impact velocity (varied between 1 and 20 m s^{-1}), angle of impact (between 5° and 90°) and the carrier rotation (±100,000 rad s^{-1}) are investigated for both elastic and sticky walls. The dispersion process shows a preferential area of drug detachment located in the southern hemisphere of the carrier. The angle of impact with the highest dispersion is 90° for the velocities over 9 m s^{-1} and between 30° and 45° for lower velocities. The rotation of the carrier before the impact, on the other hand, for velocities higher than 7 m s^{-1}, plays a little role on the dispersion performance. The DEM results are finally "distilled" into a simplified analytic model that could be introduced as a sub-scale model in Euler/Lagrange CFD calculations linking fluid dynamics with the detachment probability of APIs in the inhaler.

1. Introduction

Dry powder inhalers (DPIs) are used for drug delivery to the respiratory tracts. The drug particles, the so-called Active Pharmaceutical Ingredient (API), need to be small enough (around 1 to 5 μm) in order to reach the deeper airways of the lungs. However, high cohesion inter-particle forces in these fine powders lead generally to the formation of agglomerates [1,2] which negatively affect the dispersion of APIs in the airflow [3]. To avoid this issue, larger particles (around 50 and 100 μm) called carrier particles are normally used; the surface of the carrier particle is coated with API particles and conveyed with the breathing flow through the inhaler. Under normal conditions, high turbulence and contact with the wall of the device ensure the detachment of the API particles and an effective delivery to the lungs [4]. Despite the abundance of DPIs in the worldwide market, however, the percentage of APIs that actually reach the lungs is only between 20 and 40%. Various techniques for increasing the efficiency of inhalation devices, therefore, have been proposed: (i) narrower inlet sections that increase air velocity and the probability of particle-wall impact [5] and (ii) grid insertion that concentrates turbulence in the inhaler swirl chamber [4,5]. In addition, the formulation of the powders can also play an important role in the penetration of the particles in the airway and the presence of high ratios of porous or elongated particles has been shown to be beneficial [4,6].

Other investigations have focused on the understanding of the mechanisms induced by flow and particle dynamics in inhaler chambers. Cui, et al. [7] and Sommerfeld and Schmalfuss [8] simulated the flow dynamics in a complete inhaler system and showed that the highest velocity and turbulent kinetic energy magnitudes are located in the swirl chamber. Milenkovic, et al. [9], Milenkovic, et al. [10] studied the particle flow dynamics in turbuhalers and focused on the location of the preferential particle deposition according to their sizes and the flow velocity. Tong, et al. [2] quantified the energy generated by the inter-particle collisions and particle-wall impacts and showed that the particle-wall collision energy is the predominant factor.

For ensuring an efficient drug delivery in the lungs, the API detachment from the carrier during the inhalation also needs to be maximised. Therefore, in recent years, micro-scale modelling of API-API and carrier-API interactions has gained interest. Cui, et al. [7] simulated one APIs-carrier agglomerate exposed to laminar plug or shear flow with different velocities and highlighted three mechanisms of detachment: lift-off, rolling and sliding. Cui and Sommerfeld [11] focused on the fluid dynamic forces acting on API particles with different properties such as their numbers (i.e. the degree of coverage APIs on carrier), API size and position. They showed that the normal and the tangential forces on the

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APIs varied with the API position on the carrier and that the fluid dynamics forces acting on APIs are lower with smaller drug particles. More recently it was shown, that turbulence of the flow about the cluster carrier-APIs can remarkably enhance the detachment probability of APIs [12]. Sommerfeld and Schmalfuss [8] studied the fluid dynamics of inhaler devices (here a Cyclohaler) and the carrier particle motion in order to quantify the fluid stresses such as the velocity, the shear rate and the turbulent kinetic energy experienced by the carriers along their way through the inhaler. Their findings show the importance of the fluid forces, in particular, the transverse lift forces, on the particle velocity. Moreover, these studies revealed the extremely high wall collision rates experienced by the carriers.

Nevertheless, although all these studies give important information on fluid and particle motion in inhalers, APIs dispersion induced by wall impact remains limited to a few studies. [1,13] investigated the breakage of an APIs agglomerate (without carrier support) under different velocities, impact angles and agglomerate strengths. Using different geometries, these studies highlight the weak API-API cohesion after an impact and confirmed the key role of the wall impacts in term of impact energy. In the same way, with an API-carrier model, Tong, et al. [2,14], with an API-carrier model, investigated a number of parameters which play a role on the number of APIs detaching from the carrier after a wall impact. They showed, in particular, that the dispersion of APIs increases with the translational velocity and the angle of impact, and that the normal component of the impact velocity is the dominant factor. They also approximated the APIs dispersion performance with a cumulative distribution function of the impact energy and the adhesion energy. van Wachem, et al. [15], with a multi-scale approach, simulated the APIs dispersion with different adhesion forces. Their findings highlight the link between the properties of particles and the performance of the inhalers. They also demonstrate the relevance of using micro-scale results (APIs-carrier impact mechanisms) in a large macro-scale simulation (i.e. the inhaler device).

The aim of this work is to fill the gap between micro- and macro-scale simulations. Micro-scale models calculate the fraction of APIs detaching from the carrier given a certain impact energy, but do not relate this information to the actual hydrodynamic conditions occurring in the inhaler. Macro-scale simulations (e.g. CFD of inhalers), on the other hand, describe the hydrodynamics of the flow in the inhaler and, by means of Lagrangian particle-tracking, the trajectories of the carrier particles, but do not convert this information in a fraction of detaching APIs and, ultimately in the performance of the device. An attempt in this direction was undertaken by [16] who developed a wall collision-induced API detachment model to be used in the frame of Euler/Lagrange calculations. However, due to the high wall collision rates in inhalers, also the resulting API detachment rate was found to be very large.

In this work, the collision between a carrier-APIs agglomerate and a plane wall is modelled at the micro-scale by means of the Discrete Element Method (DEM) and the effect of impact velocity, angle of impact and angular velocity on the API detachment is investigated. The DEM results are then "distilled" into a simplified analytic model that can be introduced as a sub-scale model in Euler/Lagrange CFD calculations linking hydrodynamics with the detachment ratio or probability of APIs in the inhaler, or more in general, into multi-physics [17] simulations of the lungs airways [18].

2. Methodology

2.1. Modelling

The present study concerns the collision of carrier-API agglomerate with a plane wall which is simulated by DEM. Any fluid dynamic effects on particle motion are neglected at the moment. DEM is a Lagrangian particle tracking method where the particles are mostly treated as point masses with respect to possible fluid dynamic forces but it allows to handle multiple particle contacts and collisions (i.e. with surrounding other particles) generally in the frame of a soft-sphere collision model. Hence, here, by considering spherical particles (before and after impact), the particles move and rotate according to the Newtonian equations of motion [1].

$$m_i \frac{dv_i}{dt} = m_i \frac{d^2 r_i}{dt^2} = \sum_{i \neq j} \mathrm{F}_{i,j} + \sum \mathrm{F}_E, \tag{1}$$

$$I_i \frac{dw_i}{dt} = \sum_{i \neq j} \mathrm{R}_i \ \mathrm{F}_{i,j}, \tag{2}$$

where m_i is the mass of particle i, v_i its velocity, r_i its position, F_E the external forces, and $F_{i,j}$ the internal or inter-particle forces. I_i, w_i, and R_i, are respectively, the moment of inertia, the angular velocity and the radius of the particle i. External forces combine fluid dynamic forces acting on each individual particle (carrier and API) and external forces, such as gravity, which are however both neglected in this study.

In this work, the internal forces $F_{i,j}$ are the contact forces and account for (i) the non-adhesive elastic contact after a collision particle-particle or particle-wall based on the Hertzian theory and (ii) the adhesive contact between 2 spherical particles based on the Bradley model.

The Hertzian model consists of a normal contact force f^n and a tangential contact force f^t [19].

$$f^n = \sqrt{\delta}\sqrt{R_{eff}}\left(k_n \delta - m_{eff} \gamma_n v_n\right), \tag{3}$$

$$f^t = -\sqrt{\delta}\sqrt{R_{eff}}\left(k_t \xi + m_{eff} \gamma_t v_t\right), \tag{4}$$

where $R_{eff} = R_i R_j/(R_i + R_j)$, is the effective radius of the colliding particles i and j with radius R_i and R_j, k_n and k_t are the normal and tangential stiffness of the contact, δ and ξ the overlap and the displacement between the particles in, respectively, the normal and the tangential direction, γ_n and γ_t the normal and tangential damping coefficients and $m_{eff} = m_i m_j/(m_i + m_j)$ the effective mass of the colliding particles with mass m_i and m_j. The concepts of displacement ξ and, in particular, of overlap δ are abstract ideas that allow the DEM to calculate the tangential and normal forces occurring during collision. In reality, two colliding particles deform rather than overlap, but the idea is conceptually practical and it is going to be use also in the discussion section.

By considering elastic materials, k_n and k_t can be defined as [19,20].

$$k_n = \frac{2E_{i,j}}{3\left(1 - \upsilon_{i,j}^2\right)}, \tag{5}$$

$$k_t = \frac{2E_{i,j}}{\left(2 - \upsilon_{i,j}\right)\left(1 + \upsilon_{i,j}\right)}, \tag{6}$$

with $E_{i,j}$ and $\upsilon_{i,j}$ are, respectively, Young's modulus and Poisson's ratio of particles i and j.

The adhesive contact between 2 spherical particles is modelled after Bradley [21].

$$\begin{cases} F_B(z) = F_c, & \text{for } z \le z_0 \\ F_B(z) = \dfrac{R_i R_j}{R_i + R_j} \dfrac{16\psi\pi}{3} \left[\dfrac{1}{4}\left(\dfrac{z}{z}\right)^{-8} - \left(\dfrac{z}{z}\right)^{-2}\right], & \text{for } z > z_0 \end{cases} \tag{7}$$

where F_B is the surface force between the particles i and j at a distance z, F_c is the maximum surface force when particles i and j are in contact ($z = z_0$), 2ψ the total surface energy of both surfaces per unit area and z_0 the equilibrium separation of the particles i and j. In our simulations, z_0 is equal to $4\ 10^{-10}$ m [22], ψ is deduced from Eq. (7) for $z = z_0$, and F_c is equal to $2.58\ 10^{-7}$ N (experimentally measured via Atomic Force Microscopy AFM) [7].