

Importance of Wall Collisions for Particle-Particle Detachment in Dry Powder Inhalers, and Advanced Wall Collision Models

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Summary

This work presents tools for estimating Fine Particle Fractions generated inside Dry Powder Inhalers, by analysing detachment of drug particles from carrier particles. The trajectories of carrier particles through an inhaler are simulated using the FLUENT software for Computational Fluid Dynamics. These are analysed, by evaluating the forces that may break carrier/drug bonds. These forces, from impacts with inhaler walls or from fluid effects, are compared with carrier/drug bond strengths, measured by Atomic Force Microscopy. The comparison is in terms of torque, which is the probable mechanism for detachment. Impact torques greatly exceed fluid-based torques. This demonstrates the importance of wall collisions; several collision models are considered, including effects of spin, inelasticity and particle shape. The results show that commonly-used wall collision models are unsuitable.

Introduction

In a Dry Powder Inhaler (DPI), the particles of Active Pharmaceutical Ingredient (API) are typically attached to carrier particles, to ensure stable storage properties. An important criterion for the performance of the inhaler is therefore the Fine Particle Fraction that is delivered to the patient – in other words, the fraction of the API particles that are detached in the inhaler. Several processes may cause detachment: the sudden accelerations caused by collisions (with the inhaler walls, or with other particles), and interactions with the air flows in mid-flight. The forces generated by these processes should be compared with the strength of the carrier-API bonds, which can be measured using Atomic Force Microscopy.

Flow simulations

The current work is a sophisticated extension of flow simulations using Computational Fluid Dynamics (CFD). The flow simulations were performed using the FLUENT software (ANSYS, Inc.; Canonsburg, Pa., USA). Results are presented from earlier work on the Ultrahaler design¹ and from a test case representing a simplified inhaler design. The simulations used the Reynolds-Stress turbulence model and second-order discretisation. Flow results are shown in Figure 1.

A standard feature of commercial CFD software is the ability to simulate the trajectories of released particles in the air flow. In the current work, the trajectories of carrier particles have been analysed further, to calculate and record the detaching processes experienced by attached API particles inside the inhaler. These processes are impact-based or fluid-based.

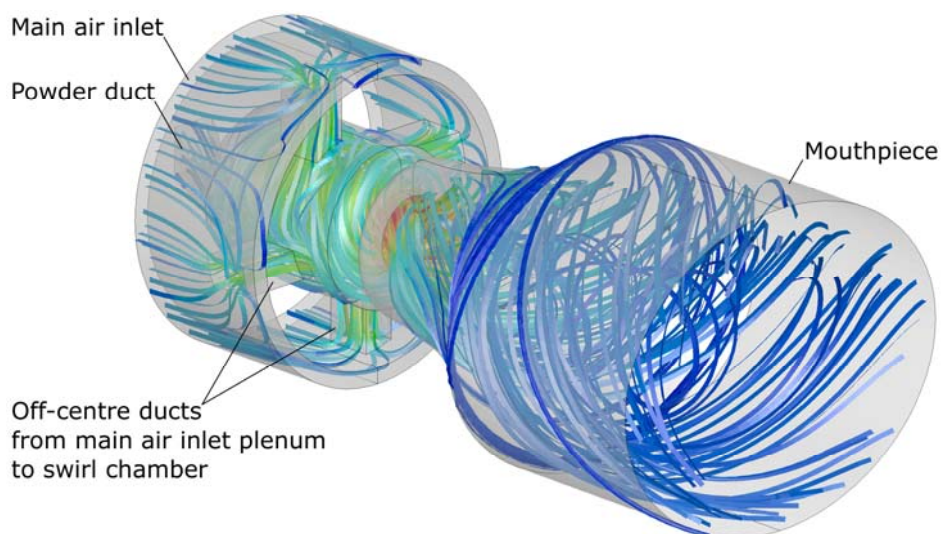


Figure 1: Pathlines of air flow in the test-case design. Air enters from the left: 90% in the outer annulus, through off-centre ducts into the swirl chamber; 10% in the powder entrainment duct (just visible behind the annulus).

Impact-based detachment

When a carrier particle collides with the inhaler walls, a detailed simulation of the collision is used to evaluate the impact experienced by attached drug particles. The simulation estimates the variations of normal force (due to the elasticity of the wall and carrier materials) and the tangential force (due to friction), as the particle impinges into the wall surface and then rebounds. The results presented below used a model that assumed the carrier particle was spherical, and included the following effects:

- rotational velocity of the particle, and its rate of change due to tangential force;
- Hertzian elasticity of the wall and carrier materials, limited by a constant yield stress, in a model for the normal force developed by Thornton and coworkers²; and
- Coulomb's law of friction.

From the simulation of the collision, the acceleration of the carrier particle is known. Force must be transmitted to the attached drug particle through the carrier/drug bond to impose this acceleration. The magnitude of the force is the product of the carrier's acceleration and the mass of the drug particle.

It should be noted that the location of the drug particle changes the force that is required. For example, suppose a carrier particle travels vertically downwards to collide with a horizontal wall. The acceleration is upwards, so a drug particle attached to the top of the carrier particle will be pressed further onto the surface. A drug particle near the bottom (but not itself colliding with the wall!) will require a tensile force – if the force required is greater than the carrier/drug bond strength, then the drug particle is effectively pulled away from the carrier. Particles on the equator of the carrier particle will be given upward acceleration by shear of the carrier/drug bond – if the bond is insufficient, the drug particles will effectively detach by shearing or twisting off the carrier. For any collision, some drug particles will be at risk of detaching while others are unaffected. The same is true of all fluid-based separation effects. In the current work, the maximum magnitude of each effect is evaluated and reported.

Fluid-based detachment

Several phenomena may cause drug particles to detach from carrier particles in mid-air, including:

- “Drag”: if the carrier/drug aggregate has a different velocity from the surrounding air, the air flow will cause a velocity gradient at the carrier particle's surface; this will generate forces on the drug particles.
- “Acceleration”: if the carrier particle accelerates due to fluid forces, then a force is required on the drug particle to ensure that it stays attached. The force's direction is generally opposite to the drag-based force.
- “Shear”: if the carrier/drug aggregate is in a region of fluid shear, this will be experienced at the carrier surface as a velocity gradient, which will cause forces on the drug particle analogous to the “drag” forces.

The magnitudes of these phenomena have been evaluated for every step in the simulated trajectories of carrier particles. Other phenomena could also be included – in particular, turbulence, which effectively causes temporary shear forces and acts similarly to the steady-state shear gradients, possibly with larger magnitude. For the acceleration term, the force needed is calculated in the same way as for impact-based acceleration. For the drag and shear effects, the velocity gradient at the surface can be converted to a tangential drag force³ and a normal lift force⁴ by approximating the carrier surface as planar. The normal lift force tends to pull the drug particle away from the carrier. However, the tangential drag force, which tends to shear or twist the drug particle from the carrier, has a larger magnitude for the small particles considered here. Also, as shown in the following section, the carrier/drug bond is more susceptible to tangential forces and torque than purely tensile lift forces.

Separation by twisting rather than pulling

An important conclusion from the work of Gutfinger and coworkers⁵ is that, when small particles are detached from a surface by fluid forces, the most likely mechanism is that the bond is broken by twisting rather than pulling. This has two main causes: first, that the lift force is less than the drag force (as mentioned in the previous section); second, that a tangential force is more likely to break a typical bond than the same force applied in a normal direction (essentially because the width of a typical bond is small compared to the dimension of the particle).

Therefore, torque has been used to evaluate the fluid-based and impact-based processes that may cause detachment, as described above. These should then be compared to the maximum torque that can be sustained by the carrier/drug bond.

Atomic Force Microscopy has been used to measure the strength of carrier/drug bonds⁶. The bond is broken by pulling the drug particle off in a normal direction; the measurement is therefore expressed as a pull-off force. To convert this to the maximum torque, further information is needed on the width of the carrier/drug contact. In the current work, the relationship between torque and pull-off is assumed to be that predicted by the JKR model⁵. This model⁷ assumes that the width of the contact area is caused by the particle deforming due to the carrier/drug adhesion. The alternative DMT model deduces a smaller moment from the same force⁵, by a factor of 2.1, for a single contact point. This is an area for further work, both experimentally and theoretically.

Results

Figure 2 shows results from previous work¹ on the Ultrahaler design of inhaler. The inhalation profile was a flowrate that linearly increased from zero to a Peak Inhalation Flow Rate of 67 L/min over 0.15s. It can be seen that there are only small regions of the inhaler where the fluid-based forces are sufficient to detach the drug particle. These regions generally correspond to high levels of all three components of the fluid-based forces: drag, acceleration and shear. A breakdown of the net force into these three components reveals that the acceleration component is generally much smaller than the drag component (typically by a factor of 2 or more), and the strain component is smaller still (typically by an order of magnitude).

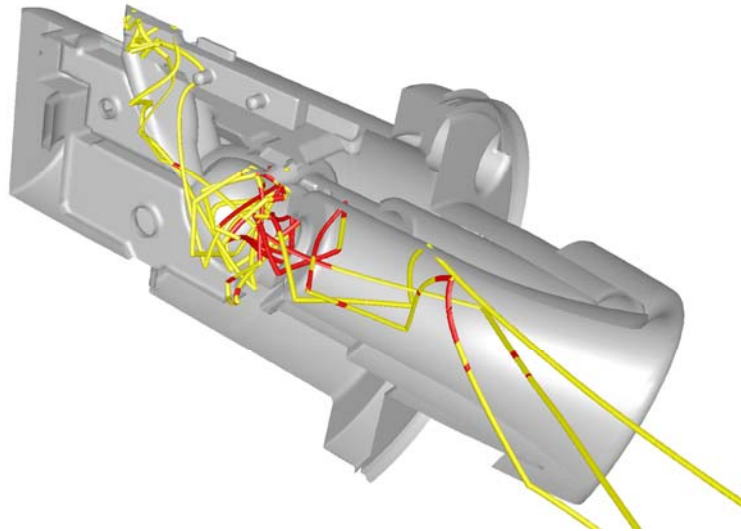


Figure 2: Trajectories of a 48µm-diameter carrier particle in the Ultrahaler. Red indicates where the fluid-based forces are sufficient to detach a 0.7µm-diameter drug particle.

All the effects show a strong dependence on the drug particle's size; this is illustrated in Figure 3. The resistance of a drug particle increases with its size (because of greater contact area with the carrier), but the torques acting on it also increase, more strongly. Therefore, the model predicts that larger drug particles are more liable to detach than smaller ones. Another conclusion from Figure 3 is that most collision events are sufficiently severe to cause detachment. However, the fluid-based effects cause detachment for only a fraction of the trajectory; the fraction is larger for larger drug particles.

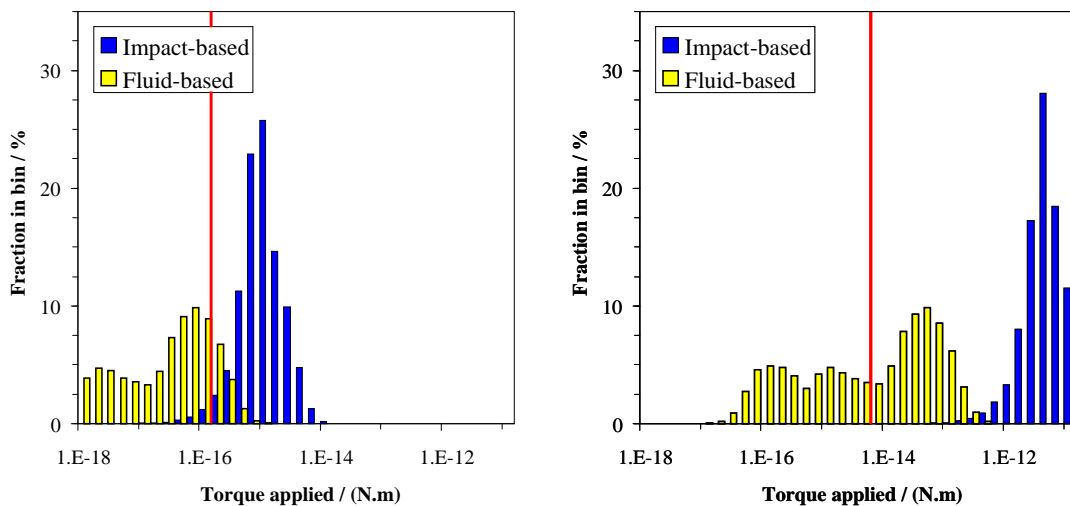


Figure 3: Distributions of torques due to impact-based and fluid-based effects, for drug particles of diameters 0.7µm (left) and 5.7µm (right), attached to 48µm-diameter carrier particles. The fluid-based distributions represent the fraction of the total trajectory time spent in each bin. The impact-based distributions represent the fraction of all impacts in each bin. The torque required to detach the drug particle (from extrapolated AFM results) is shown by the vertical red line.

Wall collision models

From the results in the previous section, it is clear that the level of detachment in the inhaler will depend on the number and severity of collisions experienced by carrier particles. Therefore, it is important that a simulation should model collisions correctly. Furthermore, it is shown below that different wall collision models can produce substantially different particle trajectories, so the wall collision model also affects all fluid-based results.

The model used to generate the results in the previous section was outlined in the section 'Impact-based detachment'; it includes the effects of yield stress and particle rotation. This is a relatively sophisticated model; in typical commercial CFD software, the standard model may assume perfectly elastic rebound with no consideration of particle rotation. However, even this sophisticated model makes the usual assumptions that the carrier particles are perfectly spherical and the inhaler walls are perfectly smooth; these are never entirely true, and carrier particles are often far from spherical. Therefore, two even more sophisticated collision models have been implemented: first, adding random fluctuations to the wall orientation, according to the model of Sommerfeld and Huber⁸, and second, simulating the collision of ellipsoidal particles, according to a new model developed by the lead author⁹. In the first case, the standard deviation of fluctuations is 6.5°. In the second case, the aspect ratio of the ellipsoids is 3.0. A few sample trajectories are shown in Figure 4. It is immediately clear that the simpler models give substantially different results. Therefore, sophisticated wall collision models are required for reliable simulation of carrier/drug detachment using the methods in earlier sections. This remains as future work.

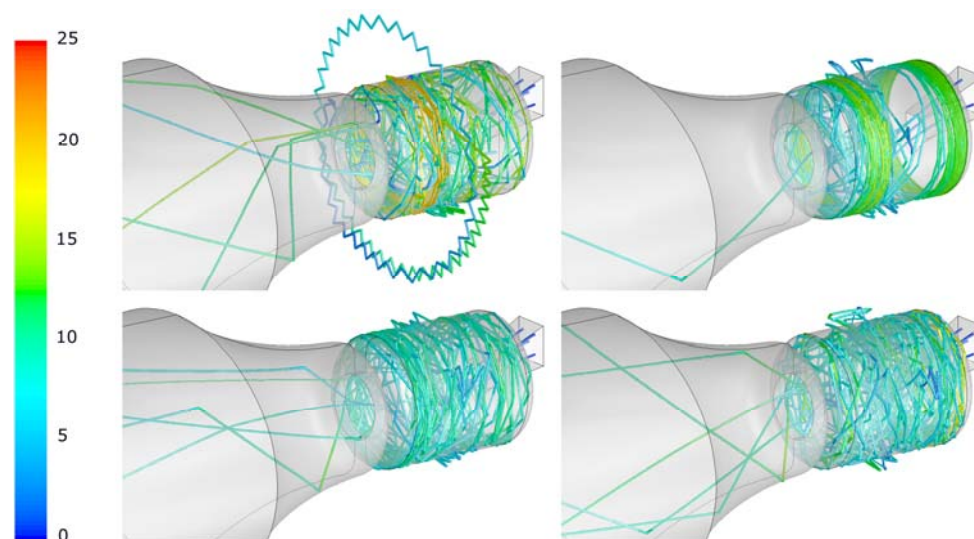


Figure 4: Simulated trajectories of 100µm-diameter carrier particles in the test-case geometry, coloured by particle speed (in m/s), with different wall collision models: perfectly elastic, ignoring particle rotation (top left); including yield and rotation (top right); including yield and rotation, with random fluctuations (bottom left); and ellipsoidal particles (bottom right). The walls of the main air inlet plenum (seen in Figure 1) are not shown, although one particle repeatedly collides with them.

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