

The Twincer geometry exploded view

Ins and Outs of Inhalers

Simulation helps optimize the performance of a dry powder inhaler for drug delivery.

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In recent years, there has been growing interest in dry powder inhalers (DPIs) as a drug delivery system that could significantly impact the treatment of diseases. The clinical applications for DPIs now extend well beyond the treatment of lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD) — which includes chronic bronchitis and emphysema — and cystic fibrosis. Recently, extensive media coverage has been given to the introduction of inhaled diabetic insulin, and research is currently

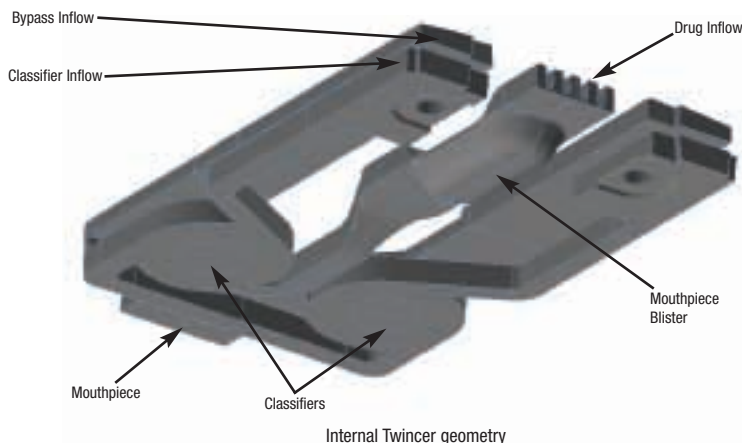
being carried out to develop methods for the delivery of antibiotics and vaccines as dry powders. A U.S. Federal Drug Administration report indicated that, unlike other drug products, the dosing, performance and clinical efficiency of DPIs may be directly dependent on the design of the device.

In order to develop biopharmaceutical drugs, like peptides and proteins, for delivery as a dry powder, two significant hurdles need to be overcome. First, the drug must be stabilized in a dry state as particles with an

aerodynamic diameter in the range 1 to 5 microns. Second, a dry powder inhaler must be developed that will efficiently deliver these microscopic drug particles to the patient. As a result of research in this area, a team at the University of Groningen in the Netherlands has developed a disposable DPI, The Twincer™, for the delivery of high drug doses. Tests have shown that the Twincer is capable of effectively delivering in a single inhalation a 60-milligram dose of pure micronised colistin sulfomethate, a drug used for the treatment of cystic fibrosis.

The Twincer holds the drug in a blister in which the tiny particles have likely joined together to form cohesive agglomerates. In order to break up these particle agglomerates, which are too large to be effective, the Twincer employs two parallel classifiers, circular chambers that apply inertial and shear forces to the particles through a carefully controlled airflow.

To accomplish this, each classifier has three tangential ports that generate





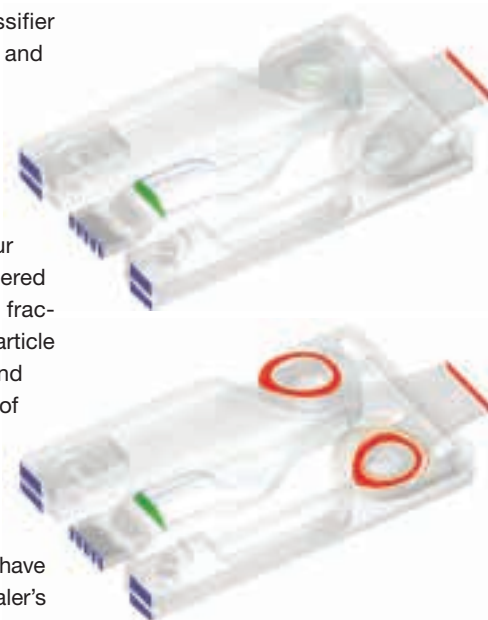
Sweeper particle retention within classifier chambers (approximately 175 micron particles)

a swirling flow within the classifier: One port delivers air from the classifier inflow; a second delivers air and entrained drug particles from the drug inflow; and a third port delivers air from the bypass channel, which functions to reduce the pressure loss of the device and, therefore, to control the effort required from the patient to make the desired inhalation. After the air and drug particles mix in the classifier chamber, they de-agglomerate and then exit the classifiers through a small opening in the base, where they join the bypass airflow and continue into the mouthpiece. The performance of the inhaler is assessed in four ways: the consistency of delivered dose, the delivered fine-particle fraction (FPF) within the dose, the particle retention within the device and the pressure drop characteristics of the device.

During experiments using the Twincer, researchers have demonstrated that minute changes in geometric details can have a significant influence on the inhaler's performance. To further understand the behavior of the inhaler and the reasons

for the design sensitivity, the team conducted a number of computational fluid dynamics (CFD) simulations using FLUENT software.

The research team took results from the CFD simulations for pressure loss and compared them with experimental measurements in order to validate the



CFD simulation showing particle trajectories for 1-micron (top) and 10-micron (bottom) particles

model. The results of both the CFD analysis and experimental work showed good agreement. Concerning the particle trajectories, the CFD analysis predicted that particles 10 microns in size and larger would be retained within the classifiers, whereas smaller particles would exit the classifiers and flow into the mouthpiece. The retained particles would include larger sweeper particles, those typically 100 to 200 microns in diameter. These predicted particle trajectories also compared favorably with experimental observation made using a laser diffraction technique. Finally, the team concluded that the drug particle cut-point is typically between 5 and 7 microns, depending on the properties of the drug and the flow rate.

The maximum dose that can be delivered by the Twincer depends on the flow split — the percentage of the total flow rate that passes through the drug inflow — and the patient's lung capacity, which may potentially be impaired. Since the design goal of the inhaler is to deliver high drug doses, the flow split within the device is of key importance. The CFD simulations showed that only 16 percent of the total airflow passed through the drug inflow and that 60 percent of the airflow bypassed the classifiers completely. These flow splits remained roughly constant over the expected operating range of the device.

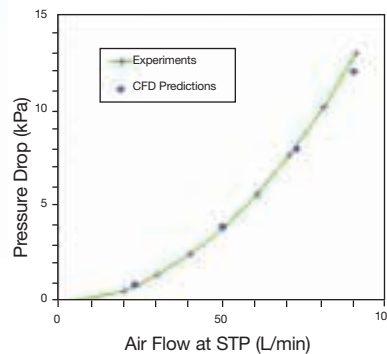
To try to improve the flow split, researchers carried out an additional CFD simulation in which a blockage was introduced into the bypass channel initially using a porous media. The team discovered that by partially blocking the bypass channel, the total airflow was reduced without affecting the mass flow available to mobilize the drug and to generate swirl within the two classifiers. From this observation, the researchers inferred that such a design change is unlikely to affect the

rate of entrainment of the drug from the blister or the rate of particle agglomerate breakup in the classifier. However, such a design change may reduce the particle exit velocity from the inhaler's mouthpiece, a condition that increases delivery of drug particles to the deep lung.

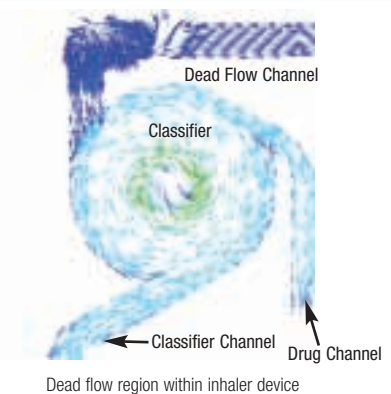
Using CFD analyses, the research team also learned that the port from the bypass channel to the classifier did not carry any flow, or was a "dead flow channel." Previously unexplained experimental observations had shown that an accumulation of particles often occurred in these flow channels. The team carried out an additional CFD simulation with these flow channels removed. As expected, the simulation showed that the removal of these flow channels had no significant impact on the performance of the device.

The use of CFD in the development of the Twincer allowed detailed assessment of the flow behavior within the inhaler. The results from the CFD analyses showed good agreement with experimental results and observations. Researchers have used the information gained from the CFD


simulations to guide design modifications of both the classifier inlet channels and the bypass flow channel. Following redesign of the inhaler prototypes, researchers again plan to use CFD simulation alongside an experimental program to further optimize the Twincer DPI. ■



CFD analysis compared with experimental data. Experimental data and CFD simulation of total air flow vs. pressure drop are in close agreement.



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