Late Breaking Abstracts

L-1 Inter-Species Comparisons of Aerosol Deposition in Imaging-Based Computational Fluid Dynamics Models of the Respiratory System

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We have developed 3D Computational Fluid Dynamics (CFD) airflow models of the respiratory system for multiple species including mice, rats, rabbits, monkeys and humans using a combination of magnetic resonance (MRI) and X-ray computed tomography (CT) imaging. These models extend from the nose/mouth to the bronchiolar region of the lung and include boundary conditions that facilitate comparisons of site-specific tissue doses for a variety volatiles and aerosols under realistic breathing/exposure conditions. For example, CFD/Lagrangian particle tracking simulations were compared in the rabbit, a species commonly used in immunology evaluations for airborne pathogens, and the human over full breathing cycles. Despite the more elaborate airway geometries in the nose of the rabbit, a higher deposition efficiency for 1 micron particles was predicted in the nose and upper airways (including the pharynx, and larynx) of the human (81.8%) than in the rabbit (53.7%) at comparable air concentrations. This greater scrubbing of particles by the upper airways in humans led to lower penetration and deposition in the tracheobronchial airways (9.97%) and deep lung (8.2%) than predicted for the rabbit (22.3% in the tracheobronchial airways and 24.0% in the deep lung). We also evaluated the influence of medical gases and breathing rates on aerosol penetration for the human. The addition of helium to the breathing air enhances deep lung penetration of 2-5 micron particles, as has been observed experimentally, with deposition patterns influenced by moments of release during inhalation phase as seen with metered dose inhalers. These models provide *in silico* tools that can be used to interpret experiments or enhance the designs of drug delivery devices as well as relate studies performed in animals to realistic human exposures. *Supported by NHLBI 2R01 HL073598, EPA EP-C-09-006, Praxair Project 52168; and DOE LDRD DOE 40403 and 46109.*

L-2 Effect of inhalation of tobramycin on reduction of hospitalisation rate in severe COPD

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Introduction: Bacterial colonization in stable disease of severe COPD and the presence of bronchiectasis can cause recurrent hospital treatment, which has a negative impact on patients prognosis. A german multicenter study investigated, if daily inhalation of tobramycin for one year will lower hospitalisation rate in severe COPD.

Methods: 44 patients with severe COPD (FEV 1 of predicted value 42.8 ±**7.**1 Tobra and 33.5±10.3 placebo) and a minimum of two hospitalisations in the year before inclusion were randomly assigned to inhale twice daily for 12 months 80 mg tobramycin or isotonic saline (placebo). Concomitant therapy according to the GOLD-guidelines. Primary end point was hospitalisation rate in the period of study, secondary end points: pulmonary function test and 6 MWD.

Results: Inhalation of Tobramycin increased hospitalisation rate from 2,8 per year to 3,5±2,7, placebo decreased the rate from 3,0 to 2,3±2,2. These differences and the results for

secondary endpoints did not reach significance. The dropout rate was high. 6 pat. (Tobramycin) and 14 pat. (Placebo) finished the study per protocol.

Conclusion:
Inhalation with 160 mg tobramycin by means of a nebulizer over a 12 month period didn`t reduce the hospitalisation rate for patients with severe COPD and a minimum of two hospitalisations compared to placebo. The severity of the disease was the main reason for the high dropout rate.

L-3 Laser diffraction method for particle sizing of high-obscuration dry powder aerosol plumes

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An understanding of the aerosol emission characteristics of a dry powder inhaler, such as particle size distribution and concentration versus time profile, helps enable the rational design of an inhaled drug product. Dispersion of a low-density spray-dried powder from a dry powder inhaler (DPI) typically produces a high-concentration optically-dense aerosol plume immediately downstream of the mouthpiece. These high-obscuration plumes challenge particle size measurement by laser diffraction. Two main problems encountered during this application are powder deposition on the optics and multiple scattering phenomena. Multiple scattering phenomena may be observed when over 10% of the particle-free zero-angle laser intensity is obscured by particles. It may be possible to use laser diffraction up to obscurations of 40% with a specialized multiple scattering correction algorithm. However, dispersed low-density powder aerosols measured immediately post-mouthpiece can produce peak obscurations exceeding 75%, yielding skewed and multimodal particle size distributions that are considered artifacts. This study introduces methods to identify and mitigate such artifacts to enable use of laser diffraction as a tool to evaluate particle size distributions of spray plumes even outside manufacturer recommended obscuration limits. A Malvern Spraytec STP2000 with custom-built optical flow cells was used to characterize high-obscuration spray-dried powder aerosols emitted from a DPI at steady flow rates of 60 to 120 L/min. To understand window fouling and high-obscuration effects, Spraytec data was exported and analyzed using a custom function to average size distributions at 5% increments of area under the particle volume concentration curve. Results demonstrated that the use of purge air and eliminating several of the smallest angle detectors from the analysis can mitigate undesirable artifacts. Therefore, for spray-dried powder formulations where drug-specific particle sizing may not be necessary, these improvements can make laser diffraction a valuable development tool for characterizing aerosol plumes directly post-mouthpiece.

L-4 Determination of film rupture characteristics for validation of numerical simulations in human airways

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To characterize the effect of dynamic viscosity on particle generation due to airway reopening during inspiration, the rupture mechanism in the peripheral airway is investigated experimentally using a simplified macroscopic model. The lining fluid in the lung containing surface active agents (“surfactant”) has a non-Newtonian, shear-thinning behavior. The used fluid Walocel,

sodium carboxymethyl cellulose (CMC), can be diluted with water to vary the dynamic viscosity. Solutions with 1.00 %, 1.25 %, and 1.50 % Walocel closely approximate the relevant similarity parameters of the lung fluid (Haslbeck 2011). The dynamic fluid viscosities are between 0.97 Pa s and 3.5 Pa s at a shear rate of 0.5 s^{-1}, and the solutions have densities and surface tensions similar to water.
With the optical method of laser induced fluorescence (LIF), the thinning process of a liquid film is investigated to determine parameters for the validation of numerical flow simulations. The liquid films are formed in an elastic ring of 17 mm diameter and deformed by expanding the ring at a constant velocity of 0.0236 m/s. The film is expanded with a stepper motor which tensions six of eight wires attached to a shaft of 10 mm diameter, and routed through rings in a horizontal plane, with the other two wires oriented parallel to the axis of the shaft. Tensioning the wires stretches the elastic ring spanning the liquid film. For LIF measurements, the fluids are mixed with the fluorescent dye Rhodamine B, and the film thinning process monitored with a high-speed camera. The results obtained using LIF indicate a critical film thickness of ~ 100 μm for the solution with a dynamic viscosity of 3.5 Pa s.
Haslbeck, K. (2011): „Entstehung exhalierter Tröpfchen in den terminalen Atemwegen.“ PhD Thesis, Leibniz Universitaet Hannover March 2011.

L-5 A Method for High-Fidelity Flow Field Characterization of Dry Powder Inhalers

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The safe and efficacious treatment of respiratory diseases often requires delivery of pharmaceutical aerosols to the lungs, using both liquid and dry powder delivery vehicles. This directs the prescribed treatment to the site of interest while minimizing systemic exposure. Dry powder inhalers (DPIs) are used to aerosolize and deliver dry powder aerosols to patients; however, the designs of these devices are often not optimal with regard to unwanted deposition both in the device and within a patient's upper respiratory tract (URT). Minimizing URT deposition requires robust DPI design based on knowledge of the powder aerodynamic size distribution and the flow field exiting the DPI device. Unfortunately, because limited experimental information on DPI flow fields is available in the literature, evaluation of current DPI designs relies heavily on computational fluid dynamics (CFD) models. Such models are often not sufficiently verified through experiment and thus may not reflect real flow behavior. In contrast, the current work introduces a systematic experimental method for evaluating DPI exit flows using a highly accurate non-invasive flow field measurement technique, i.e., time-resolved digital particle image velocimetry (TRDPIV). The TRDPIV method provides high spatial and temporal resolution of DPI flows and includes previously unavailable insight and information such as turbulence levels. This study reports a TRDPIV evaluation of the Aerolizer® inhaler, performed at a bulk flow rate of 60LPM (corresponding to ~2kPa of patient inspiratory effort) measured at various distances from the mouthpiece. The results demonstrated that the velocity profile widens as this distance increases. During inhalation, the spinning drug capsule in the device increased exit turbulence by two-fold, which could negatively affect the fundamental transport of pharmaceutical aerosols to the patient. Comparisons between TRDPIV results and published experimental and CFD results were also performed, further illustrating the accuracy of the method and insight which may be gained.

L-6 Quantitative characterization of transcriptional responses to engineered nanoparticles of different physico-chemical parameters

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Assays indicating the overall frequency of processes such as apoptosis and necrosis in a sample of treated cells are the traditional benchmarks used in toxicology studies of novel materials. However, new experimental technologies have dramatically reduced the cost of collecting high-dimensional and omic-level datasets quantifying gene expression shifts in cells and tissues. Here we use quantitative analytics to classify and correlate high-dimensional gene expression data with the results of gross toxicity assays in human cells exposed to nanoparticles of varying size and composition. Using principal component analysis, we find distinctly clustered transcriptional responses according to the surface charge of the particle, but not according to core size or specific functionalization, in agreement with previous work suggesting that nanoparticle toxicity depends principally on surface charge. However, we find that widely divergent molecular-level responses underlie this phenomenon for fullerenes as compared to CdSe quantum dots of the same charge, despite the similarity in gross response. We additionally compare the molecular responses of these nanoparticles to those of small molecules with well-characterized long-term effects. We expect this methodology to be a useful adjunct to traditional assays in classifying and predicting the toxicity of new materials.