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Abstracts: Drug Delivery to the Lungs 32

01. DIGITALISATION IN RESPIRATORY MEDICINE, WHERE ARE WE HEADING TO?

Sabine Häussermann[1]

[1]*VisionHealth GmbH, Landsberger Str 72, Munich, 80339, Germany*

Summary: Digitalisation has changed our life in many ways, and it is also changing the way we treat patients. Digitalisation has a great potential to make communication and the use of resources faster and easier. That way, digitalisation facilitates what we have done analogue before: communicate, send, and store diagnostic and lab data, visualise data in graphs etc.

An even grander potential of digitalisation lies in using artificial intelligence (AI). But AI will only get us to a certain point, the real value lies in combining AI and human emotional intelligence (EI), with that we can leverage healthcare to the next level. We might see correlations we missed before, get support for physicians in another way. In other fields such as chess, we have already seen the success: While even chess grand masters were losing against AI already in 1995, we could see that the combination of AI and human does not only beat humans (not surprisingly) but also AI. When digitalisation is done in an ethical way, the combination of digital tools, AI and physicians can lead to real personalised medicine, putting the patient into the centre.

Key Message: Digitalisation is more than translating analogue data into digital signals, sent electronically. Digitalisation bears the potential to use big data and evaluate it with artificial intelligence. With that, we can personalise medicine in a way, which was not possible before and create powerful tools for physicians.

02. INHALED THERAPIES FOR COVID-19

Peter J. Barnes, FRS, MedSci

National Heart & Lung Institute, Imperial College London

SARS-CoV-2 is a coronavirus that infects epithelial cells in the naso- and oropharynx before infecting epithelial cells of the lower airways and alveoli and in severe COVID-19 spreading systemically and inducing a systemic inflammatory response. SARS-CoV-2 is spread mainly by virus particles in droplets and aerosols. This suggests that inhaled therapies may be useful in the treatment of early COVID-19 disease before severe respiratory systemic features develop and potentially in reducing transmission of the virus in the community. To be effective any inhaled therapy must be rapidly acting to prevent viral replication in respiratory epithelial cells to prevent the disease spreading down the respiratory tract and into the systemic circulation. It also needs to be safe and available for early prescription in order to prevent severe disease and hospitalisation. The development of inhaled therapies for COVID-19 may involved repurposing of existing inhaled therapies or developing inhaled formulations of new drugs with antiviral effects.

Patients with asthma and COPD were reported to be less likely to be hospitalised with SARS-CoV-2 infection despite the concern that this coronavirus would have severe consequences for these patients as coronaviruses are known to trigger severe exacerbations. One possibility was that this may be due to the widespread treatment with inhaled corticosteroids (ICS), which are known to suppress ACE2 and TMPRSS2 on epithelial cells that are key entry receptors for the virus and also reduce virus replication in vitro. A community based open label parallel group phase 2 study of the ICS budesonide (800 μg bid until recovery) in people with early symptoms (within 7 days of onset) of COVID-19 and confirmed by PCR testing (STOIC) showed that only 1/69 people in the ICS group developed severe disease compared with 10/70 in the usual care group.[1] Clinical recovery was also shorter in the ICS group. This finding was confirmed in an open label study of inhaled budesonide in individuals over the age of 65 years at risk from severe COVID-19 (PRINCIPLE), which showed a reduction in time to recovery and a trend towards reduced hospitalisation and death.[2] Several other trials, including double-blind studies, of ICS in early COVID-19 are currently underway with different corticosteroids, including ciclesonide, which appears to be the most effective against SARS-CoV-2 *in vitro*.[3] However, a recent double-blind study of nasal and inhaled ciclesonide failed to show any benefit in early COVID-19, although the population was mainly young adults who have a low risk of disease progression.[4] The mechanism of action of ICS in COVID-19 has not yet been established, but may involve reduced viral entry due to suppression of ACE2 and TMPRSS2 in airway epithelial cells, reduced viral proliferation or reduced inflammatory mediators secreted by airway epithelial cells that may promote viral spreading.

Interferon β1 is currently approve for treating multiple sclerosis. Nebulised IFN-β1a (SNG001) gave a greater degree of clinical improvement in hospitalised COVID-19 patients and a reduction on symptoms (mainly dyspnoea) compared to with placebo and was well tolerated.[5] However, studies in early disease are underway but have not yet been reported, although there are logistical problems in the need for a nebuliser to deliver the drug. Inhaled PUL-42 is a combination of a TLR2/6 and a TLR9 inhibitors which is effective in a single inhaled dose against SARS-CoV and MERS-CoV infection in mice and reduces the lung viral load.[6] This drug is now in clinical trials for COVID-19. Other inhaled drugs, including antivirals such as remdesivir and niclosamide, are also in development.

03. PRE-CLINICAL ANIMAL MODELS: USEFUL ASSET OR A WASTE OF RESOURCES?

Mark Birrell

Imperial College London and AstraZeneca

Time and time again I hear ''preclinical in vivo models are not predictive of clinical results'' and they are blamed for the failure of research programs. Having spent 3 decades working with these models, it does tend to grind. To be fair, the statement isn't incorrect,

its more that ''we'' should be realistic of what the rodent models can really tell us. In my view the *in vivo* systems are very useful for PK/PD modelling i.e. looking for target engagement and then a related function, and linking that to exposure/dose. It's when it comes to modelling diseases that the models can fail: the lung structure, the cells, the physiology, the immunology, the mediators etc are different in rodents compare to man. Add to that is we, as yet, do not know what triggers the majority of human respiratory diseases, and, indeed they are likely to multifactorial – *precision medicine* is the rallying cry for the majority of on-going projects.

I would like to share with you some data we published a few years ago (ref below) in which we looked at the role of an ion channel expressed on airway sensory nerves, TRPV1, in chronic cough. The preclinical data was very supportive of progressing to clinical assessment but when the human study read out, the data were very disappointing. I will show you how we are currently trying to address how we can improve the predictivity of the *in vivo*

04. TARGETED NASAL DRUG DELIVERY – FOR NOSE, BODY AND BRAIN

Julie D. Suman, Ph.D.[1]

[1]*Next Breath, an Aptar Pharma company, 1450 South Rolling Road, Baltimore, Maryland / 21045, USA*

Summary: Chemoreceptors, trigeminal parasympathetic pathways and lymphatic tissue within the nasal cavity represent the future of nasal drug delivery. Targeted deposition in specific regions to deliver medication to these sites is growing. Unmet needs in CNS conditions such as Parkinsons Disease, Alzheimer's and brain cancers like glioblastoma, all my benefit from drug transport along the olfactory neurons into the cerebral spinal fluid (CSF) or brain. Narrow spray plumes and optimized instructions for use help to direct droplets to the region of interest. For example, an increase in insertion depth of the spray nozzle may improve deposition in the olfactory regions by ~30%. However, deposition alone may not be enough. Formulation strategies to overcome mucociliary clearance are being investigated to improve retention. In addition, certain mucoadhesive excipients may also potentiate the immune response for intranasal vaccine. Nanoparticulate systems have the potential for both intranasal vaccination and improving uptake in the CNS via the olfactory nerves. The optimal nanoparticle size is being investigated as well as the potential toxicity associated from increased uptake in the brain. In vitro nasal casts and imaging studies have been instrumental in understanding intranasal deposition. Additional learnings from in silico models is also advancing the understanding of targeted nasal drug delivery.

Key Message: Intranasal targeted delivery shows promises for vaccine administration and CNS therapies. An understanding of formulation optimization via mucoadhesives and nanoparticulate systems may further advance these treatment modalities.

05. NEBULIZERS AND COVID-19: AEROSOL GENERATION VS. AEROSOL DISPERSION

Rajiv Dhand, MD, FCCP, FACP, FAARC, FRSM, ATSF

Division of Pulmonary and Critical Care Medicine
Professor and Wahid T. Hanna, MD Endowed Chair of Medicine
Associate Dean of Clinical Affairs
Graduate School of Medicine
University of Tennessee Health Science Center, Knoxville, TN

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the global pandemic of coronavirus disease 2019 (COVID-19), has afflicted more than 245 million people worldwide and caused more than 5 million deaths (1). COVID-19 primarily affects the respiratory tract and infected persons generate respiratory droplets and aerosols containing the virus that transmit the infection to susceptible hosts (2). Patients with COVID-19 need inhaled therapies, either for pre-existing respiratory diseases or because of new onset respiratory distress and hypoxemia in patients with no previous pulmonary problems. Aerosolized therapies increase particle concentrations in the vicinity of patients receiving such treatments (3, 4). Inhalers (pMDIs, DPIs and SMIs) have a very low risk of contamination and the risk of spreading infection with those devices is largely due to ''bioaerosols'' generated by the patient during breathing, speaking, coughing or sneezing (2,5,6). In contrast, nebulizers, especially those that are operated continuously, release ''fugitive emissions'' that could remain in the indoor environment

06. INVESTIGATING THE EFFECTS OF FLUID COMPOSITION ON BACTERIAL AEROSOL PRODUCTION

Mathura Thirugnanasampanthar[1], Rod G Rhem[2], Myrna B Dolovich[2,3] & Zeinab Hosseinidoust[1,4,5]

[1]*McMaster University, Department of Chemical Engineering, 1280 Main Street West, Hamilton, ON, L8S 4L8, Canada*
[2]*St. Joseph's Healthcare, Firestone Research Aerosol Laboratory, 50 Charlton Ave East, Hamilton, ON, L8N 4A6, Canada*
[3]*McMaster University, Faculty of Health Sciences, Department of Medicine, 1280 Main Street West, Hamilton, ON, L8S 4K1, Canada*
[4]*McMaster University, School of Biomedical Engineering, 1280 Main Street West, Hamilton, ON, L8S 4K1, Canada*
[5]*McMaster University, Micheal DeGroote Institute for Infectious Disease Research, 1280 Main Street West, Hamilton, ON, L8S 4K1, Canada*

Summary: Airway lining mucus (ALM) is a complex hydrogel composed of 98% (w/v) water and 2% (w/v) solids content.[1] Biological aerosols, including infectious aerosols, are believed to originate from shear-stress induced breakup of the ALM. Understanding how the composition and viscoelastic properties of the ALM affects infectious aerosol production can provide valuable insight into airborne transmission mechanisms. In this study we examined the effect of fluid composition on bacterial aerosol production. Solutions containing different concentrations of peptone water, a microbial growth medium rich in protein content, were used to suspend the bacterial pathogen, *Staphylococcus aureus (S. aureus).* Peptone water solutions were aerosolized using the single jet Blaustein Atomizer module. Polydisperse bacterial aerosols were size fractioned using a viable six-stage cascade impactor. Size and counts of bacterial aerosols generated from the three peptone water solutions were compared. Mean particle size of bacterial aerosols increased as the concentration of the peptone solution was increased from 1.5% (w/v) to 5.0% (w/v) and 10% (w/v) peptone content. Additionally, the number of bacterial aerosols generated from a 1.5% (w/v) peptone water solution was significantly greater as compared to the number of aerosols produced from a 10% (w/v) peptone water solution.

Key Message: Bacterial aerosols were generated from solutions formulated to mimic the solids concentration of the ALM. Significant changes in size and quantity of bacterial aerosols were observed as the concentration of the peptone water solution was altered, demonstrating the influence of fluid composition on the production of pathogen containing aerosols.

07. AN ADAPTABLE DUAL-CHAMBER MICROFLUIDIC PLATFORM TO INVESTIGATE PSEUDOMONAS AERUGINOSA BIOFILM GROWTH AT THE AIR-LIQUID INTERFACE UNDER CONTROLLED HYDRO AND AERODYNAMIC FLOWS

Zhang Ye[1,2], Dina M. Silva[2], Daniela Traini[2,3], Paul Young[2,4], Shaokoon Cheng[1], Hui Xin Ong[2,3]

[1]*School of Mechanical Engineering, Faculty of Engineering, Macquarie University, Sydney, NSW, Australia*
[2]*Woolcock Institute of Medical Research, Sydney, Australia.*
[3]*Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, NSW, Australia*
[4]*Department of Marketing, Macquarie Business School, Macquarie University, Sydney, NSW, Australia*

Summary: *Pseudomonas aeruginosa* (*P. aeruginosa*) biofilm colonizing and growing in the human respiratory tract is a known cause of reduced antimicrobial response in several chronic respiratory diseases. Although numerous *in vitro* models have been developed to provide important insights about biofilm structure and promising treatments for biofilm-related infections, most models are still based on mono-interface culture. The handful of air-liquid interface (ALI) models developed, are incapable of manipulating the airflow dynamics, an essential feature to mimic different respiratory regions and disease conditions. The failure to reproduce the host environment may lead to misleading results. In this study we developed a dual-chamber microfluidic device and set up a dynamic platform capable of establishing an ALI model to closely mimick the lung environment. Using this platform, 48 h old *P. aeruginosa* biofilms were cultured, and their development studied as a function of nutrient supply conditions, in addition to aerodynamic shear forces. The biofilm samples were investigated in a cross-sectional study to compare their viable cell number, morphology, antibiotic susceptibility to a model antiobiotic, ciprofloxacin hydrochloride (CIP), and biofilm matrix permeability.

Key Message: Our study shows that biofilms developed in nutrient-rich conditions are thicker, less permeable, and more resistant to antibiotics compared to those grown in nutrient-depleted conditions. Under nutrient-rich conditions, mechanical shear forces induced from airflow dynamics produced thinner and less permeable biofilms, but no apparent alternation in antibiotic susceptibility were observed. Moreover, it was found that the minimum biofilm eradication concentration (MBEC) of CIP using our device was significantly higher than the conventional microtiter plate method. These findings indicate that using less physiologically relevant biofilm *in vitro* models could lead to an overestimation of drug efficacy, potentially leading to clinical failure.

08. PULMONARY DELIVERY OF BEDAQUILINE-LOADED CUBOSOMES FOR NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENT

Suyash M. Patil[1], Shruti S. Sawant[1] & Nitesh K. Kunda[1]

[1]*Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, Jamaica, NY 11439, USA*

Summary: Non-small cell lung cancer (NSCLC) is the leading cause of cancer deaths globally. The available treatment options are limited by adverse effects and development of drug resistance. Hence, newer drug candidates and drug delivery systems that have minimal adverse effects with significant anticancer efficacy are required. For NSCLC treatment, inhalation route of drug delivery is highly beneficial as it delivers drugs directly into the lungs, requires lower doses, and limits systemic toxicity. Bedaquiline (BQ), an anti-tuberculosis drug has previously shown excellent anti-cancer efficacy, but the drug's poor aqueous solubility limits its delivery via the lungs. In this project, we developed inhalable BQ-loaded cubosome (BQLC) nanocarriers for NSCLC treatment. The BQLC were prepared using a solvent evaporation technique and displayed a particle size of 150.2 ± 5.1 nm, zeta potential of (+) 35.4 ± 2.3 mV, and encapsulation efficiency of $51.85 \pm 4.83\%$. The solid-state characterization (DSC and PXRD) confirmed drug encapsulation within the cubosomes. The BQLC nanocarriers showed excellent aerodynamic properties after nebulization (MMAD of $4.21 \pm 0.53\ \mu$m and FPF >75%). The BQLC displayed enhanced cytotoxicity with a $\sim$3-fold reduction in IC_{50} compared to free BQ in NSCLC (A549) cells, after 48 h treatment. Additionally, 3D-tumor simulation studies established the anticancer efficacy of cubosomal nanocarriers as compared to free BQ.

Key Message: This is the first study exploring the potential of cubosomes for inhaled therapy. Further, the results suggest that bedaquiline-loaded cubosomes could be a promising NSCLC treatment with optimum particle characteristics, excellent aerosolization performance, and enhanced anti-cancer activity.

09. A HUMAN NOSE-ON-A-CHIP AS A PHYSIOLOGICALLY RELEVANT IN-VITRO MODEL FOR NASAL DRUG DELIVERY

Hanieh Gholizadeh[1,2], Shaokoon Cheng[2], Agisilaos Kourmatzis[3], Zara Sheikh[1], Daniela Traini[1,4], Paul Young[1,5] & Hui Xin Ong[1,4]

[1]*Respiratory Technology, The Woolcock Institute of Medical Research, Sydney, NSW 2037, Australia*
[2]*School of Engineering, Macquarie University, Sydney, NSW 2109, Australia*
[3]*School of Aerospace, Mechanical and Mechatronic Engineering, The University of Sydney, Sydney, NSW 2006, Australia*
[4]*Department of Biomedical Sciences, Faculty of Medicine, Health, and Human Sciences, Macquarie University, Sydney, NSW 2109, Australia*
[5]*Department of Marketing, Business School, Macquarie University, Sydney, NSW 2109, Australia*

Summary: A dual-channel nose-on-a-chip (NOC) was developed incorporating an air-liquid interface model of human nasal epithelial cells as a novel platform for testing nasal drug delivery *in-vitro*. The novelty of the NOC lies in mimicking realistic deposition of drug aerosols in the apical donor microchannel, where the cells are exposed to a flow-induced shear stress of 0.23 Pa, mimicking the *in-vivo* nasal airflow during inhalation. In addition, a pulsatile fluid flow within the acceptor basolateral microchannel mimics the systemic circulation through the vasculatures in the human nasal mucosa. This dynamic microenvironment significantly influences the transport profile of ibuprofen (IBU-model drug) across the nasal epithelium. The pulsatile flow in the basolateral microchannel significantly increases the rate of drug transport and the delivery of aerosolized drug under flow conditions in the apical microchannel causes a further increase in the percentage of transported IBU. Furthermore, the barrier function of the nasal epithelium remains unaffected throughout the study, as assessed by the *in-situ* transepithelial electrical resistance measurements. Hence, this NOC highlights the significant effect of the biomechanical factors such as shear stress on nasal drug delivery assay results and the importance of incorporating these physiological dynamic conditions for *in-vitro* nasal drug testing. The miniaturized

platform of the NOC with in-built electrochemical and impedance sensors is rapid and relatively economical for quantification of IBU transport and epithelial integrity, respectively. Importantly, these sensors are sufficiently accurate for the quantification of the IBU transport and comparable to current analytical methodologies.

Key Message: Nasal drug delivery testing using the physiologically relevant dynamic microenvironment recreated by the NOC demonstrated the impact of biomechanical factors such as shear stress and dynamic real aerosol deposition on drug permeability. Hence, NOC can serve as a potential alternative to the conventional static models and enhance *in-vitro in-vivo* correlations.

10. TARGETING DEEP LUNGS WITH SWELLABLE NANO/MICROGELS FOR THE DELIVERY OF SURAMIN

David Encinas-Basurto[1], Kiley McCombs [1], Ernest Vallorz[1] & Heidi Mansour[1,2]

[1]*Skaggs Pharmaceutical Sciences Center, College of Pharmacy, The University of Arizona, 1703 E. Mabel St, Tucson, Arizona 85721, USA.*
[2]*Department of Medicine, Division of Translational and Regenerative Medicine, The University of Arizona College of Medicine, Tucson, AZ, USA*

Summary: In this study, novel biodegradable cross-linked carboxymethyl chitosan (CMC) nano/microgels were developed and evaluated *in vitro* as potential carriers for sustained pulmonary suramin salt (Sur) delivery. Upon deposition, aerosols must first go through efficient aerodynamic filtration to reach the deep lung, where they must then avoid rapid macrophage clearance to grant a local sustained release. Therefore, developing swellable nano/microparticles with respirable aerodynamic diameters in a dry state but larger geometric size via swelling is a promising approach to avoid alveolar macrophage clearance and achieve high deposition. This study designed nano/microgels by spray-drying CMC for suramin salt delivery with L-Leucine (Leu) as an aerosolize enhancer molecule. Particle size distribution, *in vitro* lung deposition, and *in vitro* release profile were tested in each formulation. NGI parameters showed satisfactory aerosol properties for inhalation, with fine particle fraction (FPF) over 30%, a respirable fraction (% RF) over 80 %, and MMAD as low as 1 μm. In addition, *in vitro* dissolution test of nano/microgels exhibited sustained Sur for more than 48 h with swelled particles.

Key Message: The addition of Leu into CMC nano/microgels shows suitable properties to be used for dry powder inhalation targeting deep lung for sustain release of suramin salt and once swell, escape from macrophages clearance.

11. IMPROVING PHYSICAL AND AEROSOL STABILITY OF SPRAY DRIED HIGH-DOSE DRY POWDER INHALER FORMULATIONS

Nivedita Shetty[1,2], Heejun Park[2], Dmitry Zemlyanov[3] & Qi (Tony) Zhou[2]

[1]*Department of Small Molecule Pharmaceutical Sciences, Genentech, Inc., One DNA Way, South San Francisco, CA 94080*
[2]*Department of Industrial and Physical Pharmacy, College of Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907, USA*
[3]*Birck Nanotechnology Center, Purdue University, 1205 West State Street, West Lafayette, IN 47907, USA*

Summary: Dry powder inhalers (DPI) have been one of the most promising developments in drug delivery systems because powders tend to be more stable than nebulized solution or suspension, do not require propellants and are portable. However, delivering high-dose antibiotics through a DPI is still a challenge. Spray drying is popular for producing DPI formulations as it enables engineering of drug particles; but many spray dried compounds are amorphous in nature and physically unstable. This study aimed to develop dry powder inhaler (DPI) combination formulations of ciprofloxacin and colistin for use in respiratory infections. Effects of colistin on physical stability and aerosolization of spray-dried ciprofloxacin were examined. Our work has shown that recrystallization of amorphous spray dried ciprofloxacin led to significant changes in aerosol performance of DPIs upon storage, which cause critical quality and safety concerns. Our study demonstrated, for the first time, that co-spray drying ciprofloxacin with colistin not only enhances the physical stability of the amorphous powder formulation through intermolecular interactions, but also improves the aerosolization through surface enrichment of colistin. We have successfully incorporated synergistic antibiotics in a single particle which ensures the simultaneous delivery of combinations to the same infection sites, potentially maximizing antimicrobial synergy.

Key Message: This study provides a fundamental understanding in storage-induced physical and aerosol instability of the spray dried powder formulations. Also, it offers novel strategies to tackle both the multi-drug resistant problem and physical stability issue of spray dried formulations by combining two synergistic antibiotics into a single formulation.

12. SPRAY-CONGEALING AND WET-SIEVING AS ALTERNATIVE PROCESSES FOR THE ENGINEERING OF D-MANNITOL CARRIERS

Joana T. Pinto[1], Sarah Zellnitz[1], Tomaso Guidi[2], Francesca Schiaretti[2], Hartmuth Schroettner[3,4], Amrit Paudel[1,5]

[1]*Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 13, 8010 Graz, Austria*
[2]*Chiesi Farmaceutici S.p.A., R&D Department, Largo F. Belloli 11/A - 43122 Parma, Italy*
[3]*Austrian Centre for Electron Microscopy and Nanoanalysis, TU Graz, Steyrergasse 17/III, 8010 Graz, Austria*
[4]*Graz Centre for Electron Microscopy, Steyrergasse 17/III, 8010 Graz, Austria*
[5]*Institute of Process and Particle Engineering, TU Graz, Inffeldgasse 13, 8010 Graz, Austria*

Summary: D-mannitol has emerged as potential alternative carrier for dry powder inhalation (DPI). Herein, we explored different innovative particle engineering processes, i.e. wet-sieving and spray-congealing, to produce D-mannitol particles suitable for inhaled delivery. To evaluate the impact of these on the particle properties, the resulting powders were characterized concerning their solid-state, micromeritics and flowability. Afterwards, D-mannitol was blended with beclomethasone dipropionate (BDP) to form low dose (1 wt%) DPI formulations and the *in vitro* aerosolization performance was evaluated using a NEXThaler®. Wet-sieving generated D-mannitol particles with a narrow particle size distribution (PSD) and spray-congealing free-flowing spherical particles. The more uniform pumice particles with deep voids of wet-sieved D-mannitol were beneficial carriers to drug aerosolization, only when used in combination with 10 wt% of a ternary agent. In turn, the spray-congealed D-mannitol has shown to be promising in terms of the relative increase of deposited drug, when used without the addition of ternary agents.

Key Message: Wet-sieving generated carriers with a narrow particle size distribution and enabled better control of the number of fines in the formulation, which showed to play a critical role in the aerodynamic performance. Spray-congealing generated smooth free-flowing spherical particles able to enhance the *in vitro* aerosolization of binary mixtures.

13. USING MICROSCOPIC HIGH-SPEED IMAGING TO QUANTIFY AGGLOMERATE-TO-WALL IMPACTION IN DRY POWDER INHALERS

Athiya Azeem[1], Gajendra Singh[1], Hak-Kim Chan[3], Lunjian Li[2], Runyu Yang[2], Agisilaos Kourmatzis[1]

[1]*School of Aerospace, Mechanical and Mechatronic Engineering, The University of Sydney, NSW 2006, Australia*
[2]*School of Materials Science and Engineering, UNSW Sydney, NSW 2052, Australia*
[3]*School of Pharmacy, The University of Sydney, NSW 2006, Australia*

Summary: The lack of predictability in the performance of dry powder inhalers (DPI) has long been a challenge in the field of inhaled drug delivery. This is due to complex interactions between device and powder formulation that remain poorly understood, most notably, in the process of deagglomeration. This study demonstrates an image processing technique that is able to quantify agglomerate to wall collision events using high-speed microscopic images taken from an optically accessible device. Mannitol of particle aerodynamic diameter, $d_{50} = 2.92\,\mu$m (M3) and $d_{50} = 4.96\mu$m (M5), at a constant flow rate of 30 SLPM (inlet: 10 m/s) and 60 SLPM (inlet: 20 m/s) were used to compare the effect of particle size distribution and flowrates.

Both flowrate and particle size were found to influence collision frequencies. For M3 powder, an increase in flow rate resulted in a significant increase in collision frequency over the field of view (FOV) examined; however, as the particle size increased, the effect of flow rate diminished. It was also observed that at 30 SLPM the particle size played a more significant role in the frequency of agglomerate-to-wall collisions than they did at 60 SLPM for the location examined in this device.

Additional fields of view must be analysed in conjunction with global imaging to better understand the overall flow behaviour in future. However, these results have demonstrated the utility of advanced image processing in quantitatively characterizing agglomerate-to-wall collision events, which would ultimately correlate with the production of fine particles.

Key Message: A methodology was developed to identify collision frequency of agglomerate-to-wall impaction from high-speed microscopic images. This work demonstrates an ability to quantify significant differences that arise from change in flow rate and powder constituent size. The technique leads to an improved understanding of deagglomeration mechanisms within dry powder inhalers.

14. A PROPELLANT DISPERSIBLE TABLET FOR PREPARATION OF SALMETEROL/FLUTICASONE COMBINATION PMDIS USING LOW-GWP HFC152A

Wiktoria Wegrzyn[1],Rachael Kay & Cuong Hoa Tran

[1]*i2c Pharmaceutical Services, Cardiff Medicentre, Cardiff. CF14 4UJ. UK.*

Introduction: The current drive to produce the next generation pressurised metered dose inhalers (pMDIs) using low global warming potential (GWP) propellants presents ongoing challenges for the pharma industry. Respitab® is a propellant dispersible tablet technology, consisting of one or more jet-milled micronized active pharmaceutical ingredients (APIs) and approved inhalation excipients e.g. lactose and menthol. It is designed to overcome manufacturing challenges such as drug loss and suspension inhomogeneity, and offers flexibility in separating drug dispensing from propellant filling, which will provide advantages when utilising flammable propellants. Propellant dispersible tablets provide consistent delivered dose and efficient aerosol properties.

Research Hypothesis: To investigate the application of Respitab pMDI technology to formulate a salmeterol xinafoate (SX) & fluticasone propionate (FP) combination pMDI using the low-GWP propellant HFC 152a.

Methods: SX/FP combination product was prepared with menthol and lactose (Lac) and dispensed into plain aluminium 14 ml canisters. After crimping with metering valves, propellant HFC 152a was pressured filled into the canisters. Standard pharmacopoeial tests were conducted to determine delivered dose uniformity and aerodynamic particle size distribution (APSD).

Results and Discussion: SX/FP pMDI containing HFC 152a produced high fine particle fraction (FPF, %<5.0 μm) values and uniform delivered dose throughout product life. This development formulation was non-optimised in terms of API particle size, and excipient properties. Nevertheless, APSD profiles compared favourably with a marketed reference product i.e. Seretide.

Conclusion: Respitab SX/FP pMDI produces a consistent, uniform and high quality aerosol utilising the next generation low-GWP propellant HFC 152a.

Key Message: Respitab SX/FP combination pMDI exemplifies a novel approach to pMDI manufacture, reducing the challenges and complexities of using HFC 152a, while producing high performance pMDIs. The use of a propellant dispersible tablet enables flexible manufacturing and separation of drug dispensing from propellant filling, a significant advantage when using flammable propellants.

15. EFFECTS OF REALISTIC IN VITRO TEST FACTORS ON THE AEROSOL PROPERTIES OF METERED-DOSE INHALERS (MDIS)

Sneha Dhapare[1], Abhinav Mohan[1], Bryan Newman[1]; Mårten Svensson[2]; Peter Elfman[2]; Dennis Sandell[3,#], Larry Winner [4], Simon Berger[5], Jürgen Bulitta[5], Günther Hochhaus[5]

[1]*Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA*
[2]*Emmace Consulting AB, Scheelevägen 22, SE-223 63 Lund, Sweden*
[3]*S5 Consulting, Ekvägen 8, SE-275 62 Blentarp, Sweden; # In Memoriam, October 29, 2020*
[4]*Department of Statistics, College of Liberal Arts and Sciences, University of Florida, Gainesville, FL, USA*
[5]*Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, FL, USA*

Summary: The size of droplets and particles emitted by a metered dose inhaler (MDI), and passing through the mouth-throat (MT) region play a key role in determining lung deposition. Realistic in vitro studies that measure the amount and size distribution of aerosols exiting an anatomical MT model are expected to improve predictability of in vivo lung deposi-

tion. In this paper, we present a systematic analysis of the effects of five different in vitro test factors (MT models, inhalation profiles (IP), MT model coatings, MDI insertion angles (IA) into the MT models and MDI firing point (FP)) on the aerodynamic particle size distribution (APSD) and droplet size distribution (DSD) of three commercial MDIs using the cascade impactor and laser diffraction (LD) methods, respectively. The goal of this research was to investigate the effects of these factors on the particle size distribution of two model suspension MDIs, Flovent® HFA (fluticasone propionate, 0.22 MG/INH) and Symbicort® (budesonide, 0.16 MG/INH; formoterol fumarate, 0.0045 MG/INH) and a model solution MDI, Atrovent® HFA (ipratropium bromide, 0.021 MG/INH). MT geometries appeared to have the strongest effects on the APSD-derived parameters, while the effects of IP depended on the product type. In comparing the cascade impaction and LD methods, limited correlations were observed between MMAD, fine particle fraction <5 μm, fine particle dose <5 μm and Dv50, which were dependent on the type of product and the active ingredient.

Key Message: The MT geometry had the strongest effect on the APSD-derived parameter of the investigated suspension and solution based commercial MDIs. Overall, the effects of the investigated factors on the DSD were often product-specific and unrelated to the formulation type (i.e., suspension or solution).

16. HIGH-DOSE INHALED RIFAMPICIN POWDER FORMULATIONS: PREPARATION, IN VITRO CHARACTERIZATION AND IN VIVO EVALUATION

Prakash Khadka[1], Shubhra Sinha[2], Ian G. Tucker[1], Jack Dummer[3], Philip C. Hill[4], Rajesh Katare[2] & Shyamal C. Das[1]

[1]School of Pharmacy, University of Otago, Adams Building, 18 Frederick Street, P.O. Box 56, Dunedin 9054, New Zealand
[2]Department of Physiology, HeartOtago, School of Biomedical Sciences, University of Otago, 270 Great King Street, P.O. Box 913, Dunedin 9054, New Zealand
[3]Department of Medicine, Dunedin School of Medicine, University of Otago, P.O. Box 56, Dunedin 9054, New Zealand
[4]Centre for International Health, Department of Preventive and Social Medicine, Dunedin School of Medicine, University of Otago, PO Box 56, Dunedin 9054, New Zealand

Summary: Despite several studies on inhaled rifampicin in the literature, there have been no reports on the *in vivo* safety and pharmacokinetics of high-dose (>20 mg/kg) inhaled rifampicin. A high-dose of rifampicin is necessary to achieve drug high concentration in the lungs and the systemic circulation to treat both pulmonary and extra-pulmonary TB. While the use of high-dose of rifampicin from the oral route is associated with increased risk of toxicity including hepatotoxicity, the pulmonary delivery is an alternative approach to achieving higher drug concentration in the lungs and the systemic circulation with a lower dose than that from oral route. In this study, high-dose amorphous and crystalline powder formulations were prepared and characterized *in vitro*. Then, the safety and pharmacokinetics of rifampicin were studied after repeated administration to *Sprague Dawley* rats by intra-tracheal insufflation once daily for seven days. Among the powder formulations prepared, the amorphous and the crystalline dihydrate formulation showed better aerosolization stability compared to the crystalline pentahydrate formulations and were selected for further *in vivo* evaluations. Repeated intra-tracheal administration of high-dose rifampicin powder formulations (50 mg/kg) were well tolerated by laboratory rats and were safe to the lungs and the liver. The intra-tracheal administration of rifampicin achieved significantly higher area under the plasma concentration-time curve (AUC) compared to that from oral rifampicin at the same dose. Inhaled administration of high-dose rifampicin, therefore, has the potential to achieve higher systemic bioavailability than oral rifampicin and can be beneficial in improving TB treatment.

Key Message: Intra-tracheal administration of rifampicin results in significantly higher systemic drug bioavailability compared to the oral rifampicin at the same dose suggesting the potential of inhaled rifampicin in achieving better therapeutic effects in TB treatment.

17. RESPIRABLE POWDER CONTAINING CYCLOSPORINE A LOADED LIPOSOMES AS IMMUNOSUPPRESSIVE AGENT SUITABLE FOR LUNG TRANSPLANT REJECTION AND THE CONTAINMENT OF SEVERE LUNG INFLAMMATION

Davide D'Angelo[1], Eride Quarta[1,2], Stefania Glieca[1], Veronica Chierici[1], Giada Varacca[1], Fabio Sonvico[1], Francesca Buttini[1]

[1]Food and Drug Department, University of Parma, Parco Area delle Scienze 27/A, 43124 Parma, Italy
[2]Plumestars srl, Strada Inzani 1, 43125 Parma, Italy

Summary: The work led to the formulation of a powder of calcium phosphate coated liposomes containing cyclosporine A (CsA). The formulation was designed to reduce the dose of CsA to be administered following lung transplantation. Potentially this formulation can be used also to contain the inflammatory process due to SARS-CoV-2.

Calcium phosphate (CaP) is a material found in bones and teeth and considered non-toxic and biocompatible and this coating could reduce the recognition by alveolar macrophages and increase the cell uptake. Moreover, CaP is insoluble at physiological pH (7.4), while it solubilizes easily at pH below 5. This could favor drug release in the cell after pinocytosis and in inflamed tissues, while reducing drug release at physiological pH [1].

The liposomes produced were evaluated in terms of size, surface charge and drug loading. The presence of the CaP coating was verified by calcium titration, variation of the zeta potential and by cryogenic transmission electron microscopy (cryo-TEM). The highest loading was obtained in the formulation containing CsA at 7% (w/w). Cholesterol was added to liposomes at two different concentrations in order to improve the stability of the nanostructure and reduce the drug leakage. However, cholesterol did not bring any improvement to the formulation. The inhalation powder produced by spray drying with the best aerosolization performance (fine particle fraction of coated liposomes powder $33.69 \pm 1.6\%$ and $50.50 \pm 0.6\%$ for the uncoated liposomes powder) was obtained using a 1:3 weight ratio between liposomes and excipients using mannitol as bulking agent and 15% L-leucine.

Key Message: This work aimed to develop a respirable dry powder for inhalation containing CsA for the local treatment of lung immune diseases. CsA was efficiently loaded into CaP-coated liposomes and transformed into a respirable powder by spray-drying. The inhaled immunosuppressive product would offer multiple advantages related to drug deposition at the target site. Furthermore, the coating of the liposomes governs the release of the drug which will occur only at only at biological acidic conditions.

18. PROTEIN DPI PRODUCTION: DISCRIMINATING DESTABILISING INFLUENCES DURING SPRAY DRYING

Friederike Roth & Regina Scherließ

Department of Pharmaceutics and Biopharmaceutics Kiel University, Grasweg 9a, Kiel, 24118, Germany

Summary: Protein formulations are especially challenging since proteins tend to aggregate or denaturise easily, resulting in a possible function loss. Most protein drugs are parenteral solutions having several disadvantages; an alternative would be a dry powder formulation for inhalation. Being a dry powder the drug should be more stable and, since sterility is not necessary for inhalation, easier to formulate. In this study, chymotrypsin as model protein and mannitol as stabilising excipient were investigated to examine the influence of the drying process in a Nano Spray Dryer B-90 HP on the protein structure. The focus laid on the impact of the different stress factors during the stages of spray drying on the protein. During pumping shear forces and adsorption to tubing material, during atomisation shear forces and ultrasonic sound and during drying, air-liquid-interfaces, thermal stress and dehydration occur. All stress factors can possibly lead to denaturation or aggregation. To detect structural changes the chymotrypsin activity assay and the measurement of changes in the fluorescence emission spectra of the fluorescent dye anilinonaphthalene-8-sulfonic-acid were used. It was found that mannitol stabilises the protein against high temperatures. Different results occurred for the stages of spray-drying. The pumping process did not cause structural changes. Atomisation, however, seems to influence the protein structure, although the enzyme activity did not change. The drying did not only influence the protein structure but also caused a small decrease in enzyme activity. Further studies will be conducted to find the best production parameters to get a stable product.

Key Message: To achieve stable protein DPI products, it is important to identify destabilising factors during production to address these with stabilising excipients. Individual stages in spray drying caused different structural changes, drying even decreased enzyme activity. Mannitol stabilised the protein against heat, whereas for other stress factors excipient selection is ongoing.

19. INHALABLE CANNABIDIOL DRY POWDERS WITH ENHANCED SOLUBILITY

Waiting Tai[1], Lyndsey Leigh Anderson[2], Jonathan Carl Arnold[2], Hak-Kim Chan[1] & Philip Chi Lip Kwok[1]

[1]*Advanced Drug Delivery Group, Sydney Pharmacy School, Faculty of Medicine and Health, The University of Sydney, NSW 2006, Australia*
[2]*Lambert Initiative for Cannabinoid Therapeutics, Brain and Mind Centre, The University of Sydney, NSW 2050, Australia*

Summary: Inhalation is a promising administration method for cannabidiol (CBD) due to its higher bioavailability than that from oral delivery. The low solubility of CBD poses a delivery challenge. In this study, spray freeze dried CBD powders with enhanced solubility were produced with dipalmitoylphosphatidylcholine and a hydrophilic bulking agent (mannitol or trehalose dihydrate), referred to as Formulation M and Formulation T, respectively. Formulation M was crystalline, while Formulation T was amorphous. Both showed higher CBD solubility than raw CBD, with Formulation T having the highest value (raw CBD vs Formulation M vs Formulation T: 3.8 μg/mL vs 11.17 μg/mL vs 16.30 μg/mL). The mass median aerodynamic diameter of Formulation T was smaller than that of Formulation M (4.47 μm vs 5.56 μm), as reflected in its higher fine particle fraction <5 μm (42.7% vs 33.6%). Formulation T may thus be further tested *in vivo* and adapted to deliver other cannabinoids by inhalation.

Key Message: Both the spray freeze-dried cannabidiol dry powders with mannitol (crystalline) and with trehalose dihydrate (amorphous) were dispersible and with enhanced cannabidiol solubility.

20. DEVELOPING ANALYTICAL METHODOLOGY AND TEST APPARATUS TO STUDY DRUG DEPOSITION IN THE THROAT

Matthew Potts[1], Ben Myatt[1], Sam Apoola[2] & Peter Healey[1]

[1]*Kindeva Drug Delivery Limited, Charnwood Campus, 10 Bakewell Road, Loughborough, LE11 5RB, United Kingdom*
[2]*School of Mechanical Engineering, Leeds University, Woodhouse Lane, Leeds, LS2 9JT, United Kingdom*

Summary: Drug deposition in the mouth/throat is a common problem with many respirable medicines. To aid the development of products which reduce this deposition, suitable analytical methodology must be developed. Knowing more about where the drug is impacted within the mouth/throat can allow for greater insight into the causes of the deposition and what changes to the product may have the greatest impact on reducing this deposition. A split anatomical throat was designed, manufactured and then incorporated into analytical methodology developed to determine regional throat deposition and the fine particle mass/fraction (FPM/FPF). The methodology was developed utilising a Fast Screening Impactor (FSI) to achieve rapid screening of device prototypes and novel formulations.

Key Message: We developed novel anatomical throat apparatus and analytical methodology to accurately determine regional oropharyngeal drug deposition of inhaled respiratory medicines, enabling rapid screening of device prototypes and novel formulations. The drug deposition data is comparable to that generated using a standard OPC anatomical throat and Next Generation Impactor testing setup.

21. HFA-152A INHALER DOSE RELEASE

Alan P. McKiernan[1], Treasa M. Thomas[1] & Cathal Duignan[1]

[1]*Prior PLM Medical, IDA Business & Technology Park, Carrick-on-Shannon, N41 WK46, Ireland*

Summary: Background: With new regulations on the horizon, the industry is looking at switching inhaler propellants to greener alternatives. These new propellants may have different properties and so their effect on the dose delivery mechanics and fluid dynamics needs to be carefully studied.

Methods: We have used phase contrast X-ray imaging at a synchrotron to investigate the sump/orifice region of off-the-shelf pMDI actuators during dose release with HFA 134a and HFA152a propellants. We have used Schlieren imaging, an optical technique that is sensitive to refractive index gradients which are often present in pMDI plumes due to gas density variations, to have observe plume expansion up to 120 mm from the same commercial pMDIs.

Results: It was observed that HFA 152a drives marginally faster plumes than HFA134a despite a slightly lower vapour pressure. Propellant boiling/cavitation behaviour appears similar for both propellants. The liquid/gaseous spray cones from each type of propellant behave similarly.

Conclusions: While further investigations will certainly be undertaken by the industry in the coming years to evaluate through-life performance of shot-weight and particle size distribution, component compatibility etc. we have seen that the inhaler dose release dynamics are broadly similar between the two propellants in placebo form.

Key Message: The inhaler dose release dynamics are broadly similar between the HFA134a and HFA152a propellants in placebo form in commercial actuators which suggests that HFA152a may be a suitable greener alternative, notwithstanding other aspects of inhaler performance that need further exploration.

22. TOWARDS A MORE REALISTIC METHOD FOR MEASURING NEBULIZED AEROSOLS: MEASUREMENT OF FINE PARTICLE FRACTION DURING SIMULATED ADULT BREATHING WITH A NEPHELE MIXING INLET AND LASER DIFFRACTION WITH SIMULTANEOUS DRUG DOSE ANALYSIS

Lois Slator[1,2], Owen Currie[1], Markus Hijlkema[1] & Darragh Murnane[2]

[1]Respironics Respiratory Drug Delivery (UK) Ltd, a business of Philips Electronics UK Limited, Chichester, West Sussex, UK
[2]School of Life and Medical Sciences, University of Hertfordshire, Hatfield, UK

Summary: The pursuit of more clinically relevant in vitro tests for nebulizers and other inhalation devices continues, as the desire to demonstrate bioequivalence using in vitro data and to refine the predictions of in vivo behaviour is still an ambition. Use of laser diffraction to determine particle size with simulated breathing showed only a minimal decrease in fine particle fraction. Simultaneous measurement of particle size by laser diffractometry and delivered dose by HPLC whilst using the Nephele mixing inlet to introduce a standard adult breathing pattern was assessed and compared to the same parameters recorded under continuous flow extraction. A small decrease in fine particle fraction was observed when a breathing profile was introduced, in line with the previous observations. A much larger percentage decrease in the delivered dose was recorded, even with the sampling time corrected for time spent inhaling. This results in a fine particle dose in the range reported by Svensson et al. in 2018. This outcome suggests that the observed decrease is mainly due to a reduction in drug being delivered to the test system and only slightly due to a change in the aerosol particle size distribution.

Key Message: The reduction in fine particle dose observed when using the Nephele mixing inlet compared to the pharmacopeial method is primarily due to a reduction in drug delivered, whilst the fine particle fraction of that drug is only slightly reduced.

23. IN VITRO INVESTIGATION INTO FUGITIVE AEROSOL FROM A NOVEL 4TH GENERATION ADAPTIVE AEROSOL DELIVERY (AAD) SYSTEM

Adam P Metcalf, Steven P Cowley & Lucy EA Hardaker

Respironics Respiratory Drug Delivery (UK) Ltd, a business of Philips Electronics UK Limited, Chichester Business Park, City Fields Way, Chichester, PO20 2FT, United Kingdom

Summary: The recent Covid-19 pandemic has drawn attention to the amount of fugitive aerosol that is emitted by nebulizers. The novel I-neb Advance Adaptive Aerosol Delivery (AAD) System incorporates an improved AAD algorithm intended to reduce treatment times compared with earlier AAD devices. We conducted an in vitro test to determine the amount of fugitive aerosol that is emitted from the I-neb Advance (AAD) System. Three production equivalent investigational I-neb Advance nebulizers fitted with non-metering chambers were filled with 1.7 mL of 2 mg/mL salbutamol solution. The delivered dose was collected on a filter during operation into a simulated breathing pattern (Tv = 500mL, I:E = 1:1, f 15 bpm). A second filter was fixed 1 cm away from the exhalation port of the nebulizer with an extraction flow of 60 L/min. Each nebulizer was run in triplicate. Salbutamol on filters was quantitated by high performance liquid chromatography. The delivered doses had low co-efficients of variation, intra-nebulizer = 0.83 to 3% and inter-nebulizer = 0.77%. The fugitive aerosol was lower than the limit of quantification of the assay (0.18% of fill) in 2/3 of the tests. Measurable exhaled doses were all below 0.3% of the fill volume. The improved AAD algorithm used in the I-neb Advance (AAD) System delivered precise, reproducible doses with minimal fugitive aerosol emissions into a simulated breathing pattern. The minimization of fugitive aerosol emissions demonstrated by AAD nebulizers likely has an added relevance to aerosol treatment following the emergence of the Covid-19 pandemic.

Key Message: The novel I-neb Advance (AAD) System was shown to deliver reproducible doses of drug with minimal (<0.3% of the nominal dose) fugitive aerosol emissions. This observation could be important in clinical situations where there is a need to minimise escaping aerosol from nebuliser devices during use.

24. AERODYNAMIC PARTICLE SIZE DISTRIBUTION AND DELIVERED DOSE EFFICIENCY OF A CONTINUOUS-OUTPUT MESH NEBULISER AND A NOVEL BREATH-ACTUATED DEVICE USING TERBUTALINE SULPHATE

Edgar H. Cuevas Brun, Huei-An Tsai, Ciou-Ting Wang, Yuan-Ming Hsu & Ke-Ting Chen

HCmed Innovations Co. Ltd., Rm. B, 10F., No.319, Sec.2, Dunhua S. Rd., Taipei City, 10669, Taiwan

Summary: The integration of breath actuation in a mesh nebuliser has introduced new solutions that can achieve higher levels of drug delivery efficiency, while reducing the emission of fugitive aerosols. As several novel treatments involving biologic drugs tend to choose liquid formulations to protect the stability and bioactivity of inhaled drugs post-nebulisation, nebulisers have encountered a growing field for their implementation in the development of combination products. The scope of this study was intended to compare the aerosol performance and delivered dose efficiency of a continuous-output mesh nebuliser and a novel breath-actuated device using terbutaline sulphate nebulising solution. Aerodynamic particle size distribution studies revealed that both devices were capable of delivering appropriate fine particle fractions (continuous output = 50.1 ± 0.9%; breath actuated = 64.7 ± 0.4%), with the breath-actuated device generating a higher percentage. The delivered dose testing using a breathing simulator to mimic an adult breathing pattern showed that the delivery efficiency of the breath-actuated nebuliser was more than twice that of the continuous-output nebuliser, reaching 88% and presenting a much lower residual mass. As aerosol was generated during inhalation only with breath actuation, the treatment time of the breath-actuated nebuliser was longer when loading the same volume of medication in both devices, as it was foreseeable. The novel breath-actuated nebuliser presented in this study was shown to provide a promising performance for its use in drug-device combination products that may require high delivery efficiency, adequate aerosol characterisation for lung deposition, and low residual mass to treat diseases by delivering drugs directly into the respiratory system.

Key Message: The novel breath actuated mesh nebuliser AdheResp® generated a high delivered dose and good fine particle fraction data compared to a similar continuous-output nebulizer. The data indicate that the AdheResp will be a suitable device for delivering drugs to the lungs.

25. IS A PRESSURE DROP ≥10 CM H_2O WITH ANY DRY POWDER INHALER (DPI) A REASONABLE THRESHOLD ABOVE WHICH A PATIENT SHOULD RECEIVE AN ADEQUATE LUNG DOSE: METHOD VALIDATION AND EXPERIENCE WITH A SAMPLE COHORT OF COPD PATIENTS?

Mark W Nagel[1], Jason A Suggett [1] & Jolyon P Mitchell[2]

[1]Trudell Medical International, 725 Baransway Drive, London, Ontario, N65 5G4, Canada
[2]Jolyon Mitchell Inhaler Consulting Services Inc., 1154 St. Anthony Rd., London, Ontario, N6H 2R1, Canada

Summary: It has been claimed that an adequate lung dose should be received above a threshold pressure drop of 10 cm H_2O with any DPI, based on the negative pressure generated by the patient's inspiratory effort. We report first the validation of a volumetric flow sensor/recorder simulating adult inhalation in accordance with a standard sinus flow rate-time waveform. We then used this sensor as validated to record flow profiles from 5 patients with varying severity of COPD familiar with the Turbuhaler* DPI, inhaling from a placebo Turbuhaler*, representing a DPI having medium flow resistance. Maximum inspiratory pressures were 19.2, 11.5, 12.7, 33.3 and 50.0 cm H_2O for patients A to E. In the laboratory, we recreated each inhalation profile via the breathing simulator-anatomical model oropharynx coupled to the mouthpiece of a Symbicort* Turbuhaler* DPI. The simulator was located distal to a microbial collection filter, positioned at the exit of a model adult oropharynx, to capture medication likely to have deposited at the carina and therefore potentially available for lung delivery. The corresponding mass of budesonide and formoterol components ($n = 3$ replicates, mean ± SD) recovered from the model mimicking these inspiratory flow rate-time profiles varied widely from 13.6 ± 3.3 to 35.3 ± 1.4 μg budesonide and from 0.7 ± 0.1, to 1.8 ± 0.1 μg formoterol. These findings highlight the value in discussion around what is an 'adequate' lung dose and what other factors, in addition to pressure drop, may be involved.

Key Message: This laboratory simulation re-created previously generated inhalation profiles from COPD patients to assess medication delivery from the same medium resistance DPI via a model oropharynx to a collection filter with highly variable outcomes that were related to inhalation duration and maximal inspiratory pressure.

26. EFFECT OF AN INHALATION CHAMBER WITHOUT INSPIRATORY VALVE AND FACEMASK FOR NEONATES USE ON DRUG DELIVERY.

Myriam Eckes and Brenda Hervieu, Lina Fontaine & Thierry Porée

OptimHal-ProtecSom, 24 rue du Train Renard, 50700 Valognes, France.

Summary: The aim of this study was to evaluate *in vitro* aerosol delivery from a pressurized metered dose inhaler (pMDI) and inhalation chamber without inspiratory valve for neonatal patients compared with classic valved holding chambers (VHCs). The effect of mask holding duration to the model face on drug delivery was also investigated and measurements were performed with different numbers of breathing cycles after each pMDI dose release. Emitted drug mass was measured using a breathing simulator and aerodynamic particle size distribution (APSD) was determined with an *in Vitro in Vivo* Correlation (IVIVC) model from data collected with a cascade impactor at a constant flow of 15L/min. For both sets of measurements, the tidal breathing pattern of a neonatal patient was recreated by a breathing simulator. Inhalation chambers with facemasks were applied on an infant face model with a 0.8 kg force. Salbutamol sulfate, fluticasone propionate and beclomethasone dipropionate, were administered in separate experiments through the inhalation chambers. The aerosol dose delivered with the inhalation chamber without inspiratory valve was observed to be about 50% higher than the aerosol dose delivered with the classic valved holding chamber. The delivered drug dose increased with the number of breathing cycles after each pMDI dose release up to 14 cycles, corresponding to 16.2 seconds mask holding duration. Using an inhalation chamber without inspiratory valve increased the delivered drug dose and the facemask holding duration after each pMDI actuation has an impact on drug delivery.

Key Message: Removing the inspiratory valve of an inhalation chamber increases both *in vitro* delivered drug with a pMDI and fine particle dose (< 5 μm aerodynamic diameter) deposited to a filter distal to a neonatal model.

27. MACHINE LEARNING APPROACH TO PREDICT THE FORMATION CO-AMORPHOUS SYSTEMS FOR INHALATION THERAPY

Sarah Zellnitz[1], Elisabeth Fink[1] & Amrit Paudel[1,2]

[1]Research Center Pharmaceutical Engineering, Inffeldgasse 13, Graz, 8010, Austria
[2]Institute for Process and Particle Engineering, Graz University of Technology, Inffeldgasse 13, Graz, 8010, Austria

Summary: The treatment of chronically obstructive pulmonary disease (COPD), asthma and tuberculosis requires a multidrug therapy applying different active pharmaceutical ingredients (APIs). In order to reduce the drug dose variability while administering the combination products to patients, the generation of co-delivery systems like co-amorphous systems (COAMS) is suggested. Co-amorphous systems have recently gained considerable interest in the pharmaceutical field for tackling poor solubility of drugs. In order to facilitate and enhance the screening for COAMS for inhalation therapy, a machine learning (ML) approach is presented herein to predict the formation of potential COAMS. A training dataset of 254 systems was built based on available literature data on COAMS and non-COAMS. Based on the training dataset, a predictive ML model was built with a predictability of 80%. The resulting ML model was validated with 21 rows of validation data (not included in the training dataset), which resulted in a predictability of 76%. This model was then used to predict the formation of COAMS in API-API combinations of 37 common APIs used in the treatment of the aforementioned lung disease. The predicted class of these 666 possible API-API combinations was analysed and put in correlation with the original dataset. Positive predictions were weighted by their distance, with predicted co-amorphous API-API combinations further from the training data considered with more uncertainty. This provided a rating amongst all predicted COAMS from which the top 100 systems were taken into consideration. Taking conventional medication regimen into account, the number of promising combinations was further reduced. Promising predicted combinations for COAMS will be selected and tested experimentally in order to validate the prediction.

Key Message: Based on molecular descriptors of a training dataset a predictive machine learning (ML) model was established (predictability 80%) and validated with 21 additional rows of data (predictability 76%). This model could succesfully be used to predict the formation of promising co-amorphous API-API combinations to be used in the treatment of lung disease.

28. INVESTIGATION OF DESIGN FEATURES ON THE PERFORMANCE OF 3D-PRINTED DRY POWDER INHALERS. PART 1: GRID MESH

Yuqing Ye[1,2], Ziyi Fan[1], Ying Ma[1,2] & Jesse Zhu*[1,2]

[1]*University of Western Ontario, 1151 Richmond Street, London, N6A 3K7, Canada*
[2]*Ningbo Inhale Pharma, 2260 Yongjiang Street, Gaoxin District, Ningbo, 315000, China*

Summary: The study on inhaler performance through modified inhalers with homogeneous aperture size across the full grid structure have been carried out. In our research, the size of each small opening except the four in the corners of inhaler grid was kept constant, and the wire splitting the grid was designed to vary, thus generating grids with same aperture size but different voidage (Figure 1). In addition, instead of injection moulding method, a novel 3D printing technology was employed to fabricate the modified inhalers, which is rarely studied. Therefore, the primary objective for this work is to investigate the influence of grid mesh voidage on inhaler performance, as well as confirming the feasibility of 3D-printed inhalers for pulmonary drug delivery. For the assembled 3D-printed inhaler with a voidage of 68.7%, the Fine Particle Fraction (FPF) was raised to 37.2 compared with the inhaler with a voidage of 13.2% and FPF of 33.8%. There was a rising trend of FPF and delivered dose when grid voidage increased, which attributed to less drug impacting on the meshes of grid and more drug passing through the apertures. The experimental results were also coupled with computational fluid dynamics (CFD) analysis, which provided a complementary understanding of the drug delivery performance differences.

Key Message: Modified inhalers by 3D-printing method, with constant aperture size across the full grid structure, were successfully fabricated and assembled. Inhalers with an increased voidage had higher *in-vitro* drug delivery performance and lower air resistance, which was proved by enhanced powder residues in the devices and more centralized powder jetting verified by CFD.

29. DETERMINATION OF AN APPROPRIATE DOSE RATIO OF A SYNERGISTIC COMBINATION OF LONG-ACTING BRONCHODILATORS FOR THE MAINTENANCE TREATMENT OF ASTHMA AND COPD

Elena Menchi[1], Charaf El Khattabi[2], Olivier Denis[3], Stéphanie Pochet[2], Karim Amighi[1] & Nathalie Wauthoz[1]

[1]*Laboratory of Pharmaceutics and Biopharmaceutics, Faculty of Pharmacy, Université libre de Bruxelles (ULB), Boulevard du Triomphe, B-1050 Brussels, Belgium, Elena.Menchi@ulb.be*
[2]*Pharmacology, Pharmacotherapy and Pharmaceutical Care, Faculty of Pharmacy, Université libre de Bruxelles (ULB), Boulevard du Triomphe, B-1050 Brussels, Belgium*
[3]*Immune Response, Sciensano, Rue Engeland 642, B-1180 Brussels, Belgium*

Summary: *Introduction.* The combination of inhaled drugs used in maintenance therapy of non-communicable respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) has shown significant improvement in symptoms and pulmonary function. As the co-administration of a long-acting β2-agonist (LABA) with a long-acting muscarinic antagonist (LAMA) could provide synergistic benefit on airway smooth muscle relaxation, pharmacological interactions between formoterol fumarate dihydrate (FOR) and tiotropium bromide monohydrate (TIO), and indacaterol maleate (IND) and TIO were studied using an *ex vivo* technique. *Methods.* An experimental model of isolated perfused guinea pig tracheal rings was used to highlight the dose ratios generating strong synergistic interactions that could be used in the formulated combinations. Recorded data were analysed with two widely used pharmacological models, the Bliss independence (BI) theory and the unified theory. These enable the synergy to be identified by accurate statistical analysis and the magnitude of interaction to be quantified, respectively[1]. *Results.* Synergistic interactions were found among the dose ratios tested, with the maximum interaction magnitudes for FOR:TIO 2:1 (w/w) and IND:TIO 10:1 (w/w). *Conclusion.* The dose ratio showing the strongest synergy and leading to the best dose reduction when compared with the same drugs as monotherapy will be chosen to be formulated. However, this synergy at the selected dose ratio requires to be confirmed on a preclinical model of asthma or COPD by assessing lung function.

Key Message: It was proposed that dose ratios of LABA/LAMA (w/w) combinations resulting in synergistic airway relaxation were highlighted using an appropriate *ex vivo* model of isolated perfused guinea pig tracheal rings. This was done to optimise the benefits of the co-administration of these drugs in the treatment of asthma and COPD.

30. A PREDICTIVE MODEL TO EXPLORE THE EFFECTS OF PHYSICOCHEMICAL PROPERTIES ON MESH-NEBULISATION

Annabel Flook[1], Daniel Lock

[1]*University of Bath, Claverton Down, Bath, BA2 7AY*

Summary: Understanding the effects of three physicochemical properties of formulations: surface tension, conductivity and viscosity, on vibrating-mesh nebulisation has previously employed a 'one variable at a time' (OVAT) approach. These formulations have used a range of components as physicochemical property modifiers and, as such, inter- and intra-literature comparisons are unsuitable for the exploration of physicochemical property interactions and their influences on nebulisation. Using Design of Experiment (DoE) methodology, a predictive model has been developed to parameterise and independently adjust the three physicochemical properties in the form of a generic formulation. The prepared formulations were hypothesised to replicate the output rate (OR) of any formulation with equivalent physicochemical properties in Vectura's FOX® vibrating-mesh nebuliser device. The model successfully mapped three active formulations to their parameterised generic formulations. When nebulised, two generic formulations adequately replicated the OR of their active counterparts (a protein-based formulation and a mucopolysaccharide), whereas one generic and active formulation pair (a small molecule formulation) showed a large difference in OR. Therefore, the three physicochemical properties alone were deemed unsuitable as predictors of OR for every formulation. The impact of viscosity on OR was also assessed. When comparing formulations comprising of the same components (the generic formulations), a strong linear relationship was observed. However, this relationship was not applicable to formulations comprising of differing components (the active formulations) and suggest caution should be exercised when comparing the OR of different formulations with respect to their physicochemical properties. Alternative properties, such as interfacial tension, should be explored to fully understand nebulisation and advance formulation development approaches.

Key Message: Three generic formulations were prepared to mimic the physicochemical properties: viscosity, surface tension and conductivity of three active formulations. When nebulised, they did

not always show comparable output rates, suggesting alternative physicochemical properties may give a better indicator of a formulation's nebulisation performance, leading to improved formulation development.

31. IDENTIFICATION OF POTENTIAL ANTIOXIDANT DEGRADATION PRODUCTS AS EXTRACTABLES FROM AN INNOVATIVE THERMO PLASTIC ELASTOMER USED IN METERED DOSE INHALERS

Jonathan Marie, Bruno LE CORRE & Claire CANNETTE

APTAR PHARMA Route des Falaises 27100 Le Vaudreuil France

Summary: Thermo Plastic Elastomers (TPEs) are used for the manufacturing of inhalation devices in the pharmaceutical industry. Antioxidants are often added to the plastics to prevent the degradation of the polymers or to protect them during the molding process. Due to the influence of different factors such as oxidation (e.g. air, water), these antioxidants may be degraded to form oxidation degradation products, which could migrate into the drug formulation as leachables. It is thus very important to identify these potential degradation products to verify the absence of any toxicity risk for patients. The work herein details, through the sample preparation and analytical LCMSQTOF analysis process, how such degradation products have been identified. The comparison of several extraction techniques for sample preparation are presented. This case study uses a novel thermo-plastic elastomer, COC 920, a low extractable, low water vapor transmission and efficient static leakage barrier material used in Aptar Metered Dose Inhalers (MDIs).

Key Message: Potential extractables from a novel TPE gasket used in MDIs were isolated by various extraction techniques and identified.

32. UNDERSTANDING IMPACT OF FINES ON FLOW BEHAVIOR OF LACTOSE BLENDS WITH AND WITHOUT MAGNESIUM STEARATE AND ITS IMPACT ON FILLING USING MEMBRANE FILLING TECHNOLOGY

M. Mehta[1], E. Sternberger-Ruetzel[1], H. Peters.[2] & O. Imole[3]

[1]*Harro Höfliger Verpackungsmaschinen GmbH, Helmholtzstraße 4, 71573 Allmersbach i.T, Germany*
[2]*DFE Pharma, Transistorweg 5, 6534 AT Nijmegen, The Netherlands*
[3]*Hosokawa Micron B.V., Gildenstraat 26, 7005 BL, Doetinchem, The Netherlands*

Summary: Filling low amount of powders for inhalation into blisters is a challenging process. Limited knowledge is available on the use of magnesium stearate as ternary agent in inhaled formulations and its effect on the filling of powders into the blisters. A study was initiated to understand the interaction of lactose fines and magnesium stearate on the flow and the filling of powders into blisters. The particle size fraction below 30μm showed a strong correlation with the compressibility and permeability of the lactose and lactose magnesium stearate blends. An increase in this fraction increases the compressibility, permeability and the fill weight of the powders. Blends having permeability values higher then 6, consistently showed lower relative standard deviation values (below 3.0%) in fill weight. This insight will help to develop robust dry powders for inhalation.

Key Message: Strong correlations have been found between lactose particles below 30μm and compressibility as well as permeability for blends with and without magnesium stearate. For the membrane filling systems, permeability and compressibility are important parameters to tune the relative standard deviations and mean fill weight.

33. INFLUENCE OF MATERIAL AND CAPSULE FILLING PROCESS WITH MINIMA® ON AEROSOLIZATION PERFORMANCES BY DPIS

Annalisa Bianchera[1], Ayça Altay-Benetti[1], Francesca Buttini[1], Pietro Pirera[2] & Ruggero Bettini[1]

[1]*Food and Drug Department, University of Parma, Parco Area delle Scienze 27/a, Parma, 43124, Italy*
[2]*I.M.A. Industria Macchine Automatiche S.p.A. Unipersonale, Via Emilia 428-442, 40064 Ozzano dell'Emilia (Bologna), Italy*

Summary: Material characteristics and filling process have significant consequences on aerosolization performances of DPIs. Different settings of a bench-capsule filler, Minima®, were compared by means of a design of experiment to identify most significant parameters affecting capsule weight among bed powder height, compression and dosage volume. Four types of lactose were used as coarse fraction in binary mixtures with micronized lactose to simulate low dosage API for inhalation. Mixtures with three dosages of fine lactose, namely 2%, 5% or 10%, were prepared for filling capsules, to study aerosolization behaviour of low-dose DPI products, which are of particular interest for lung administration. Data indicate that Minima® provides consistent results, in terms of weight and repeatability. Compression was identified as the main parameter affecting both final weight and emitted fraction after capsule discharging by DPI RS01. On the other hand, the type of raw material mainly influences the fine particle fraction, with Lacto-Sphere® MM50 showing the best performances, with the 2% of fine lactose.

Key Message: The effect of capsule filling parameters on emitted dose and fine particle fraction by a DPI was investigated using a tabletop device for capsule filling. Compression was the parameter that affected weight and emitted fraction the most, while the type of coarse lactose seems to influence the fine particle fraction.

34. CO-AMORPHIZATION: A FORMULATION STRATEGY FOR AMORPHOUS HIGH DOSE DRY POWDER TO TREAT LUNG INFECTIONS

Bishal Raj Adhikari[1], Keith C. Gordon[2] & Shyamal C. Das[1]

[1]*School of Pharmacy, University of Otago, Dunedin 9054, New Zealand*
[2]*Department of Chemistry, University of Otago, Dunedin 9016, New Zealand*

Summary: High dose antibiotic dry powder has become a treatment approach for effectively treating lung infection in various pathophysiological lung conditions such as cystic fibrosis and non-cystic fibrosis bronchiectasis. This has kindled further interest in reformulating other antibiotics as dry powder to potentially optimize therapeutic outcomes. Among different techniques used for the preparation of such high dose dry powder, spray drying is a promising technique, particularly due to its particle engineering capability. However, in many cases, the technique produces particles in an amorphous state which tend to have poor aerosolization and chemical stability. Here, co-amorphization with amino acid was explored as a potential strategy to overcome limitations associated with spray drying. Ceftazidime, a potent antibiotic against *Pseudomonas*

aeruginosa, was used as a model drug and valine was used as a model amino acid to prepare a co-amorphous system. The formulations were characterized using various known techniques of spectroscopy, microscopy, and thermal analysis. X-ray diffraction and infrared spectroscopy suggested that the ceftazidime-valine (CeV) formulation was amorphous and co-amorphization was evident through calorimetry. SEM images suggested increased asperities in CeV formulation. Valine was found to effectively improve the fine particle fraction of spray-dried ceftazidime by 24%. In addition, it improved the chemical stability of the drug by 24%. This study concludes that amino acids can be used to achieve dual edge in terms of aerosolization and chemical stability.

Key Message: To treat lung infections, highly aerosolizable high dose amorphous antibiotic dry powder with improved chemical stability can be prepared by co-amorphization with valine using co-spray drying technique.

35. BUDESONIDE SOLUTION MDIS: PLASMA TREATED CANISTER PERFORMANCE AND OTHER CANISTER TYPES

David A. Lewis[1], Rob. D. Johnson[1], Daniel I. Lewis[1], Jacqueline Green[2]

[1]Oz-UK Limited, Chippenham, Wiltshire, UK
[2]Presspart Mfg Ltd, Blackburn, UK

Summary: Drug delivery performance and chemical stability has been evaluated for an ethanol-based budesonide solution HFA 134a MDI formulation packaged within five alternative canister types. The chemical stability of the budesonide was observed to be directly dependent upon canister choice.

Following 3-months valve-up storage at 40°C/75%RH, surface treated canisters (plasma, anodised and FEP) were observed to have a budesonide residual of 97.3 ± 0.5%, 97.5 ± 1.3% and 97.6 ± 0.6% respectively. However, under the same conditions the drug residual for the same formulation packaged in non-surface treated stainless steel and aluminium canisters was much lower; 65.5 ± 0.3% and 88.6 ± 0.6% respectively.

With regards to drug delivery performance, when packaged in Plasma treated canisters, no significant difference ($p > 0.05$) was observed in budesonide drug delivery metrics (delivered dose, fine particle dose and MMAD) before and after 3-months valve-up storage at 40°C/75%RH.

The data presented in this study highlights the importance of selecting a suitable canister type during formulation and product development. With regards to the budesonide formulation evaluated in this study, surface treated canisters (plasma, anodised and FEP) outperformed plain stainless steel and plain aluminium canisters.

Key Message: A solution Metered Dose Inhaler (MDI) budesonide formulation has been evaluated in five alternative canister types. The chemical stability of the budesonide is observed to be directly dependent upon canister choice.

36. FLUTICASONE PROPIONATE SUSPENSION MDIS: PLASMA TREATED CANISTER PERFORMANCE AND OTHER CANISTER TYPES

David A. Lewis[1], Rob. D. Johnson[1], Daniel I. Lewis[1], Jacqueline Green[2]

[1]Oz-UK Limited, Chippenham, Wiltshire, UK
[2]Presspart Mfg Ltd, Blackburn, UK

Summary: Selection of a suitable canister during Pressurised Metered Dose Inhaler (MDI) product development is of primary importance. Canister material and surface treatment has a direct influence upon drug chemical stability and formulation physical stability. Adhesion of drug(s) to a canister's surface during a product's shelf-life or canister's use-life will affect drug delivery performance metrics including content uniformity of the delivered and therapeutic dose.

This study evaluates the drug delivery performance and chemical stability of a Fluticasone Propionate suspension within HFA 134a in various canister types: Fluorocarbon Polymerised (FCP) Plasma treated, Anodised, Fluorinated Ethylene Propylene (FEP) coated, Stainless Steel, and Aluminium. The drug delivery performance was observed before and after 3-months storage of the MDIs at 40°C and 75%RH. At the 3-month time point, no significant difference was observed between the performance of plasma treated canisters and FEP coated canisters ($p > 0.05$); both of which out-performed non-surface treated canisters. When compared to Flixotide (FPD = 44.1 ± 4.7 μg) data collected during this study, no significant difference ($p > 0.05$) was observed after 3-months valve-up storage at 40°C and 75%RH in the FPD ≤5μm for plasma treated canisters (FPD = 40.4 ± 0.8 μg) and FEP coated canisters (42.2 ± 1.6). However, significant difference ($p < 0.05$) was observed for the uncoated plain aluminium canister following storage (FPD = 33.5 ± 1.1 μg).

Key Message: A Fluticasone Propionate suspension within HFA 134a was evaluated in various canister types for drug delivery performance and residual drug total can content. No significant difference was observed in the performance of plasma treated canisters and FEP coated canisters ($p > 0.05$); both of which out-performed non-coated canisters.

37. A DESIGN OF EXPERIMENTS APPROACH TO OPTIMISING SPRAY DRYING YIELD AND PRODUCTION EFFICIENCY OF A MODEL INHALED POWDER FOR GLOBAL HEALTH APPLICATIONS

Andrew J.L. McArthur[1], Victoria L. Oliver[2], Pete Lambert[1], Eddie French[1], Jacob Harker[1] & Michelle P. McIntosh[1]

[1]Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmacy and Pharmaceutical Science, Monash University, Melbourne, VIC 3052, Australia.
[2]Melbourne University School of Population and Global Health, Melbourne University, Melbourne, VIC 3052, Australia.

Summary: Pharmaceutical products developed for low-income markets may face greater challenges in covering manufacturing costs while meeting affordable costs of goods in these settings. Inhaled products for these markets must address the cost of manufacture and how this impacts the affordability of the product to the end-user in order to improve chances of long-term sustainable healthcare outcomes. In this example of an inhaled powder product designed for use in low-income markets, addressing the cost of manufacture require optimisation of the raw yield and speed of production spray drying process by increasing process parameters such as the concentration of feed solution and feed solution pumping speed. However, increasing powder production in this way may influence the carefully engineered powder particle characteristics which in turn will affect dose delivery. To address this issue, the complex nature of the relationships between spray drying processing parameters and physical powder attributes critical to product performance were characterised using a Design of Experiments (DoE) approach. Response Surface Methodology (RSM) was then employed to construct a predictive model and carefully optimise the processing parameters for maximal powder yield and spray drying efficiency while maintaining tight limits on particle size, moisture content, and glass transition temperature.

Key Message: A DoE (2^4-CCD) approach was used to increase spray drying yield and powder production efficiency while maintaining critical quality attributes of trehalose powder particle for deep lung penetration, in order to better address inhaled product affordability challenges experienced by low-income countries.

38. FORMULATION, CHARACTERIZATION AND OPTIMIZATION OF DRY POWDER FOR INHALATION USING COMBINED MICRONIZED LEVO-DROPROPIZINE AND CURCUMIN

Carlotta Giulieri[1], Gianluca Trentin[2], Stefano Cagliero[2] & Aurelie Schoubben[1]

[1]*University of Perugia, via del Liceo 1, Perugia (PG), 06123, Italy*
[2]*Aptuit an Evotec company, via Alessandro Fleming 4, Verona (VR), 37135, Italy*

Summary: Aim of the current work was to optimize process and composition of previously studied Dry Powder for Inhalation (DPI) using anti-tussive Levo-Dropropizine as Active Pharmaceutical Ingredient (API). The previous work based on Design of Experiments (DoE), was performed to select a carrier-based formulation of Levo-Dropropizine, studying different grade of Lactose, different concentration of Magnesium Stearate, Drug Load (DL) and blending procedure. However, micronized Levo-Dropropizine with selected formulation didn't give satisfactory inhalation performance. During the present work co-micronization with Magnesium Stearate and replacement of fine carrier with micronized Curcumin demonstrate to improve API inhalation performance. Surprisingly, less agglomeration between particles by co-micronization technique, shape similarity of micronized Curcumin with fine Lactose and usage of it as carrier into the formulation, improve aerosolization of Levo-dropropizine. Several formulations were produced, studying different combination and composition to better understand the impact of each component. Micronized and co-micronized APIs were characterized by High Performance Liquid Chromatography (HPLC), Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), Scanning Electron Microscopy (SEM) and Laser Light Scattering (LLS). Blends and capsules were manufactured and characterized by Blend Homogeneity (BH), FT4 Rheometer, Next Generation Impactor (NGI) and Dosage Unit Sampling Apparatus (DUSA). Promising results were obtained with reduced agglomeration behaviour followed by increase of ED, FPF and FPD with reduced retention of material inside capsules, device and mouthpiece.

Key Message: Co-micronization process of Levo-Dropropizine and Magnesium Stearate reduced the micronized API agglomeration. Furthermore, thanks to shape similarity between micronized Curcumin and fine Lactose Monohydrate, Curcumin was used as carrier in DPI formulation of Levo-Dropropizine. The combination of these two approaches, permitted a deeper increase of inhalable particles of Levo-Dropropizine.

39. FUNDAMENTAL PROPERTIES OF PROPELLANT AEROSOLS CAN GUIDE TRANSITION TO LOW GLOBAL WARMING POTENTIAL PMDIS: SIZE, VELOCITY AND SURFACE CHARGE

Irene Rossi[1] & William J. Ganley[1], Philip Chi Lip Kwok[2], Ivan Zadrazil[3], Graham Hassall[3], Olivier Michelet[4], Segolene Sarrailh[4], Guillaume Brouet[4], Robert Price[1] & Jagdeep Shur[1]

[1]*Nanopharm Ltd, An Aptar Pharma Company, Cavendish House Hazell Drive, Newport NP10 8FY*
[2]*Sydney Pharmacy School, Faculty of Medicine and Health, University of Sydney, Pharmacy and Bank Building A15, NSW 2006, Australia*
[3]*Dantec Dynamics, Garonor Way, Royal Portbury, Bristol, BS20 7XE*
[4]*Aptar Pharma, Route des Falaises, 27100, Le Vaudreuil, France*

Summary: Lower global warming potential (GWP) propellants (hydrofluoroalkane, HFA, 152a and hydrofluoroolefin, HFO, 1234ze) are readily available replacements to those currently employed in life-saving medications (HFA 134a and 227a). This study aimed to investigate fundamental physical properties of aerosols emitted from pMDIs using currently employed propellants and low GWP alternatives. The net surface charges for all propellants were positive, however HFO 1234ze generated near-neutral charges of both polarities, with HFO being the least bipolar propellant. However, water content was higher for this propellant as result of storage conditions and contribution of sub-assembly components (valve, canister, and actuator). Net charge may determine relevant differences in aerosol deposition and, therefore, should drive formulation development approaches. The droplet diameter and velocity for the different propellants fell into multiple groups (for example: the two low GWP propellant droplets were larger at short distances from the actuator). This information will guide the use of excipients to achieve desirable performance of products reformulated using these propellants. Finally, the results evidenced as well the influence of valve and actuator's material components on the net-charges developed. Therefore, device sub-assembly components play an important role during pMDI re-formulation and development.

Key Message: The fundamental properties of currently used and new low GWP propellants have been characterised. Differences in aerosol droplet surface charge were observed for HFO 1234ze. Moreover, low GWP propellants droplets were larger at short distances from the actuator. These may determine relevant differences in aerosol deposition, which can be balanced by formulation composition.

40. INVESTIGATION ON THE IMPACT OF RESONANT ACOUSTIC MIXING PARAMETERS AND CARRIER TYPE ON THE DEPOSITION PATTERNS OF BUDESONIDE/FORMOTEROL FUMARATE DPI COMBINATION PRODUCT

S Radivojev[1,2], M Beretta[1,3], V Reinisch[1], V Rehbein[1], J T Pinto[1], E Frönlich[1,2], & A Paudel[1,3]

[1]*Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 13, Graz, 8010, Austria*
[2]*Center for Medical Research, Medical University of Graz, Stiftingtalstraße 24, Graz, 8010, Austria*
[3]*Institute of Process and Particle Engineering, Graz University of Technology, Inffeldgasse 13, Graz, 8010, Austria*

Summary: Dry powder inhalers (DPIs) are commonly used systems for the delivery of inhaled therapeutics. Most of the available DPI systems consist of larger carrier excipient particles (in the size range of 100-150 μm) mixed with the micronized drug (typically 1-5 μm), resulting in a complex interplay between (i) selecting proper blending parameters (ii) identifying the optimal carrier particle properties, as well as (iii) selecting the most appropriate device for delivery. Therefore, the aim of this study was to evaluate the blending parameters necessary to produce homogeneous blends of a Budesonide (BUD)/Formoterol Fumarate (FF) DPI. For this, a resonant acoustic mixer was used and short blending times (30 and 90 s) combined with different acceleration levels (30, 45 and 60 g) were applied. Two different carriers were used (α-lactose monohydrate (αLH)

and mannitol (MAN)), while the aerosolization performance was investigated using two types of inhalers, namely Cyclohaler® (CH) and Novolizer® (NOV). Finally, the predicted deposition patterns were evaluated. We found that for αLH blends, homogeneity was achieved with lower blending times compared to MAN containing ones. Nevertheless, the selection of MAN as a carrier in a combination with NOV resulted in the improvement of the aerodynamic performance of the BUD/FF combination therapy. *In-silico* modelling of the deposition profiles showed that different formulation strategies, resulted in comparable fractions of the delivered to the peripheral (P) and central (C) region of the lung yet different in the extra-thoracic region (ET). This could be relevant when designing formulations intended for a localized therapeutic effect.

Key Message: Investigation of the process parameters and carrier types showed that MAN combined with reservoir type of device could deliver higher amounts of drugs to the lungs. The developed deposition model showed the relevance of investigating further subtle differences present in aerodynamic performance data when developing a DPI formulation.

41. A HIGH FORCE PMDI FOR DELIVERY INTO THE OLFACTORY REGION OF THE NASAL CAVITY

Andy Cooper[1], Barzin Gavtash[1]

[1]*Kindeva Drug Delivery, Charnwood Campus, 10 Bakewell Road, Loughborough, Leicestershire LE11 5RB*

Summary: A high force nasal pMDI has been designed which enables greater penetration and deposition of the spray within the nasal cavity. This may be useful for targeting nose-to-brain delivery via the olfactory region.

In-vitro data suggests a step change in spray penetration versus current commercial nasal pMDI products, which are less feasible for deep nasal cavity delivery. The high force and expected lower plume temperature, of the new device, may though present additional discomfort for the patient.

Further work is also required to establish the performance of the high force nasal pMDI with a range of formulations and nasal cavity geometries.

Key Message: A nasal pMDI has been designed to generate higher force than current commercial nasal pMDI products. This enables greater penetration of the spray within the nasal cavity, which may be useful for targeting nose-to-brain delivery via the olfactory region.

42. THE APPLICATION OF MORPHOLOGICAL FILTERS IN AUTOMATED IMAGING FOR NASAL FORMULATIONS: A DESIGN OF EXPERIMENT APPROACH

Paulo Serra[1], Jared Hall[1], Irene Rossi[1], Jagdeep Shur[1] & Robert Price[1]

[1]*Nanopharm Ltd, An Aptar Pharma Company, Cavendish House Hazell Drive, Newport NP10 8FY, United Kingdom*

Summary: Particle size distribution (PSD) is possibly one of the most important critical material attributes (CMAs) in bioequivalence studies for nasal spray. The use of automated imaging, combined with Raman spectroscopy (MDRS), allows to measure the PSD of each component present in the formulation individually. The aim of this study was to highlight the importance of morphological filters application for MDRS method development and how they can be efficiently selected though a screening Design of Experiment (DoE). Twenty two different filters combinations have been used to analyse Flonase® formulation (fluticasone propionate, FP and microcrystalline cellulose - MCC). Only one single combination (number 10) showed a good power of particle selection, proven also by Raman identification: only 6 particles of microcrystalline cellulose been picked as potential FP particles between the one screened by the filters applied. Results obtained showed that and approach by a screening DoE can lead to a quickly defined working set of filters for the measurement of just API particles in nasal spray. A further DoE for optimization of these parameters will increase the method efficiency of particle detection. Moreover, the same approach will be applied to nasal formulations comprising suspended proteins and peptides in order to show the importance of filters and automated imaging combined with Raman for PSD and morphological analysis of such complex products.

Key Message: Application of morphological filters in automated imaging allows to more efficient and time-cost effective development of a suitable method for characterization of complex nasal spray suspensions in bioequivalence study. Particularly, a screening DoE was useful to select the most relevant filters for identification and PSD determination of API in Flonase® formulation.

43. DEVICE AND FORMULATION FACTORS AFFECTING THE AEROSOL PERFORMANCE OF PRESSURISED METERED DOSE INHALERS

B. J. A. Thorne[1], S. B. Kirton[1], M. Knowles[2] K. C. Lee[3], D. Murnane[1], A. I. Sapsford[2], A. D. Wright[2]

[1]*University of Hertfordshire, College Lane, Hatfield, AL10 9AB, U.K.*
[2]*Bespak Europe Ltd., Bergen Way, King's Lynn, Norfolk, PE30 2JJ, U.K.*
[3]*University of East London, Docklands Campus, University Way, London, E16 2RD, U.K.*

Summary: An experimental study was conducted to determine the key device and formulation properties and their interactions affecting the spray performance of pressurised metered dose inhalers (pMDIs). A two-level, 2^3Taguchi Orthogonal Array was constructed as part of a design of experiments approach to maximise the variation in the response variables whilst minimising the required number of experiments. Spray orifice diameter, actuator sump volume, orifice length, metering chamber volume, propellant and ethanol fraction were varied in the current study, with volume-equivalent droplet diameter, spray area, plume angle and ovality as the response variables. Droplet mass median aerodynamic diameter, spray orifice diameter and ethanol fraction exhibited the most significant influence. Propellant type, sump volume and metering chamber volume had the largest impact on spray area measured at a distance of 30 mm from the tip of the actuator mouthpiece. The plume angle and ovality were not well described by the input variables in the current study, remaining an interesting area for future investigation.

Key Message: Droplet diameter and spray area are key performance metrics to be met when designing pMDI products and were well predicted by the device and formulation properties varied in the present study.

44. DEVELOPMENT OF A NASAL SPRAY CONTAINING A NOVEL HUMAN RECOMBINANT ANTIBODY FOR SARS-COV-2 THERAPY

Antonia Zapata del Baño[1], Cyrine Mestiri[1], Hank Oviatt[2], Bill Zimlich[2], Eric Mathur[2], Karen Terry[3], Robert Price[1], Jagdeep Shur[1], Irene Rossi[1]

[1]*Nanopharm Ltd, An Aptar Pharma Company, Cavendish House Hazell Drive, Newport NP10 8FY, United Kingdom*
[2]*Diomics Corporation, 41083 Sandalwood, Murrieta, CA 92562, United States*
[3]*Aptar Pharma, 250 North Route 303, Congers, NY 10920, United States*

Summary: A novel human recombinant antibody for prophylactic treatment against SARS-CoV-2 was formulated in a nasal solution comprising chitosan as mucoadhesive polymer. Two levels of protein concentration have been assessed and formulations loaded into Aptar VP3 nasal pump. The formulations produced showed values of pH (6.2-6.3) and osmolality (414 and 421 mosm/kg) suitable to prevent precipitation of the antibody in the final solution and for nasal administration. Assay of the protein after formulation manufacturing showed a lower dimeric fraction than the reference standard and hydrodynamic diameter of the final formulations was also comparable to the unprocessed antibody solution (10 nm). Zeta-potential values were higher than 25 mV, indicating colloidal stability against aggregation due to charge stabilization for the formulations obtained. Spray performance did not evidence any difference between protein levels in the final formulations when combined with VP3 nasal pump. Particularly, droplet size distribution (mean volume diameter of 55.13 μm for the low dose formulation and 57.21 μm for the high dose), spray pattern and plume geometry resulted to be applicable for nasal delivery. Finally, for both solutions sprayed antibody content was within 75-125% of the target delivered dose with a very low variability on ten consecutive shots (5%). Future studies will assess the formulations stability under refrigerated and ambient storage conditions of the combination product and of the antibody comprised in the formulation, whereas *in vivo* studies will define pharmacokinetics and pharmacodynamics profile of these final formulations.

Key Message: The possibility to deliver to the nose a novel human antibody for prophylactic treatment against SARS-CoV-2 employing Aptar VP3 pump was assessed. Spray performance of the formulations manufactured was characterized and no protein agglomeration was observed in the formulations and after spraying, indicating favourable results in applying this system for delivery of antibodies to the nose.

45. HOW DOES THE TONGUE INFLUENCE TRANSPORT OF INHALED PARTICLES FROM A PRESSURIZED METERED DOSE INHALER (PMDI) AND VALVED HOLDING CHAMBER (VHC)

Mark W. Nagel[1], Jason A. Suggett[1] & Jolyon Mitchell[2]

[1]*Trudell Medical International, 725 Baransway Drive, London, Ontario, N65 5G4, Canada*
[2]*Jolyon Mitchell Inhaler Consulting Services Inc., 1154 St. Anthony Rd., London, Ontario, N6H 2R1, Canada*

Summary: An *in vitro* study was undertaken to assess what changes occurred to the aerosol deposition patterns from a pMDI (fluticasone propionate (FP); 125 μg/actuation) delivered alone or via an AeroChamber* Plus Flow-Vu* VHC/mouthpiece, when the tongue was intentionally omitted from a model anatomic adult oropharynx. A modified fast screening abbreviated Andersen impactor (T-FSA) operated at 28.3 L/min ±5% sampled the aerosol emitted at the exit of the oropharynx of the model-on-test, to capture the size profile of medication likely to have deposited past the carina and therefore potentially available for lung delivery. The pMDI alone simulated 'perfect' coordination with no delay while a 2-s delay was simulated following pMDI actuation when the VHC mouthpiece was attached to the model. Five replicate measurements were made with the models with and without the tongue present in the oropharyngeal cavity with 5 doses delivered per measurement. FP was recovered from the pMDI actuator, VHC interior, model airway, as well as the T-FSA and assayed by a validated HPLC-spectrophotometric procedure. The pMDI alone deposited 81.6 ± 10.9 and 64.0 ± 5.1 in the oropharyngeal airway with and without tongue respectively, causing the mass delivered to Stage 5 (1.1- 4.7 μm) to increase from 11.7 ± 1.5 to 35.5 ± 1.0 μg. Delivery via the VHC demonstrated a smaller difference between the mass of FP recovered from Stage 5 (29.6 ± 6.1 – tongue present vs. 36.5 ± 2.2 μg – tongue absent), indicating less impact on likely lung dose.

Key Message: Tongue position can affect lung delivery of aerosolized medications. We compared aerosol deposition within an adult oropharyngeal model compared to a modified version where the tongue structure was removed. We showed tongue presence can impact aerosol deposition, although the magnitude of the effect is reduced when a VHC is present.

46. LEVERAGING DPI FORMULATION SCREENING: PARTICLE-PARTICLE INTERACTION

Raquel Borda d' Água[1] & João Pereira[2]

[1]*Hovione, Estrada do Paço do Lumiar, Campus do Lumiar, Edifício R, 1649-038, Lisboa, Portugal*

Summary: Dry powder inhalers (DPIs) have attracted enormous attention worldwide due to its local targeting, rapid drug effect and reduced systemic toxicity. However, DPI formulations consist of highly cohesive powders that tend to agglomerate. Therefore, fine and coarse carriers are often used to reduce the cohesion and promote the flowability and aerosolization. Understanding the role of cohesive-adhesive forces in different formulations and establishing a predictive approach for aerodynamic particle size distribution (aPSD) is thus, highly beneficial, since the traditional Next Generation Impactor (NGI) is a complex and time-consuming technique. The purpose of this study is to explore the relationship between powder dispersibility with the aerodynamic performance of different DPI formulations. For this, formulations with different ratios of drug substance/fine lactose/coarse lactose were tested using a laser diffraction technique (Sympatec HELOS/RODOS) and NGI. Sympatec was used to characterise powder dispersibility and inherent cohesion and adhesion forces at different pressures. The aerodynamic profile was characterized using an NGI at a pressure drop of 4kPa with a commercial inhaler. A correlation was evaluated between the powder dispersibility obtained using Sympatec and the aerodynamic properties from the NGI analysis.

Key Message: A simple and innovative solution was developed for faster DPI formulation screening.

47. PLUME FRONT VELOCITY AND FORCE TO ACTUATION CHARACTERISATION OF PRESSURISED METERED DOSE INHALERS AND SOFT MIST INHALERS

Joshua Houlden[1], Miles Jeanneret[1]
Davide Cunha[1] & Mervin Ramjeeawon[1]

[1]*Intertek Melbourn, Saxon Way, Melbourn, Herts, SG8 6DN, UK*

Summary: There has been increased focus on the generic pharmaceutical industry when embarking on in-vitro only bio-equivalence testing of inhaled products, using a weight of evidence based approach to submission. In the draft product specific guidance document for beclomethasone dipropionate issued in May 2019, the FDA proposed additional supportive in-vitro studies. These included the characterisation of Plume Front Velocity (PFV) profiles of the test and reference product to support the weight of evidence approach to negate the need for resource consuming comparative clinical endpoint bioequivalence studies [1].

Plume Velocity analysis is a technique that permits the movement of the plume generated from the inhalers to be visually captured over time from which data can be extracted and extrapolated to determine the velocity of the plume emitted.

Two different commercially available metered dose inhalers (pMDI) and one commercially available soft mist inhaler (SMI) were selected to demonstrate this novel approach to device characterisation. The differences in the plume velocity between the two different device types (pMDI/SMI) was investigated and the comparison of plume velocities between a generic pMDI device and its reference listed drug (RLD). The force to actuate, and plume duration times, for both pMDIs were also investigated.

Key Message: Development of Plume Front Velocity and Force to Actuate methodologies for the characterisation of pMDI and SMI devices using the Proveris SprayVIEW were shown to be highly effective for the evaluation of emitted aerosol devices and in-vitro bioequivalence studies between generic and reference listed drug products.

48. INFLUENCE OF GEOGRAPHY ON THE CARBON FOOTPRINT IMPACT OF BREEZHALER® DRY POWDER INHALER

Aumônier S[1], Mezzi K[2] Whiting A[1] & Fulford B[2]

[1]*ERM, Eaton House, Wallbrook Court, North Hinksey Lane, Oxford, OX2 0QS, UK*
[2]*Novartis Pharma AG, Novartis Campus, Basel, Switzerland*

Summary: Inhalers have a significant contribution to the carbon footprint (CFP) of healthcare. Novartis is committed to reduce the environmental impact of its product and in line with this commitment, the Breezhaler® device is available as a hydrofluoroalkane/chlorofluorocarbon–free dry powder inhaler for delivery of asthma medications.

This paper presents the findings of the cradle-to-grave CFP studies of two Breezhaler® inhaled combinations (indacaterol acetate/mometasone furoate [IND/MF] and IND/glycopyrronium bromide/MF [IND/GLY/MF]) from Italy and Spain; additionally, a conservative estimate, which can be used as a reliable proxy for CFP of Breezhaler® in other countries, is also reported. The Breezhaler® combinations assessed were IND/MF (30-day pack, without digital companion), IND/GLY/MF (30-day packs, with and without digital companion) and IND/GLY/MF (90-day pack, without digital companion).

The Breezhaler® combination of IND/GLY/MF (without digital companion) has the lowest CFP among all the combinations evaluated. Similar CFP estimates were reported for all the Breezhaler® portfolio products in the most conservative estimate and the countries evaluated.

Active pharmaceutical ingredients, inhaler production energy and packaging are the main contributors to the CFP; for IND/GLY/MF, 30-day pack with digital companion, the raw materials of the digital companion have the highest contribution. Excipients, distribution, and end-of-life stages all make minimal contributions to the CFP of Breezhaler® products.

Overall, the low CFP of the Breezhaler® portfolio (which has fixed dose combinations of IND/MF and IND/GLY/MF) is not influenced by geography and the findings from Italy, Spain and the conservative estimates are all consistent with the published literature from other countries.

Key Message: The Breezhaler® portfolio (which has fixed dose combinations of IND/MF and IND/GLY/MF) has a low carbon footprint (CFP) across the world. Even at the most conservative estimate, the CFP of Breezhaler® is low and consistent with footprints of countries evaluated in this study (Italy and Spain) and in previous studies (France, Germany, Japan, and UK).

49. THE QUANTITATIVE ASSESSMENT OF VAPE DEVICES AS NOVEL PULMONARY DRUG DELIVERY SYSTEMS USING FLUORINE-18 RADIOLABELLED DRUG MOLECULES

George Herbert[1,2], Glenn Woolley[1,2,3], Dave Roberts[1,2], Juozas Domarkas[1,2], John Wright[1,2], Graham Wright[3] & Stephen J. Archibald[1,2]

[1]*Department of Biomedical Sciences, The University of Hull, Cottingham Road, Hull, HU6 7RX, UK*
[2]*The Positron Emission Tomography Research Centre, The University of Hull, Cottingham Road, Hull, HU6 7RX, UK*
[3]*Hull University Teaching Hospitals NHS Trust, Castle Hill Hospital, Castle Road, Cottingham, HU16 5JQ, UK*

Summary: Positron emission tomography (PET) is a highly sensitive and quantitative modality that can be employed for the efficient and informed development of novel pulmonary drug delivery devices. Vape devices present an alternate drug delivery system whereby the performance and formulation can be personalised for the end-user to improve experience and compliance. A novel molecule was designed, synthesised and radiolabelled to allow efficient radiolabelling of vape liquid. This probe was used to understand the influence of device settings on output. It was concluded that a high a temperature setpoint (315°C), low coil resistance (< 0.3 Ω) and short vape duration (≤ 4s) greatly increased output whilst flow rate (2.3 – 35 L/min) and glycerol content (0 – 100%) had little influence. Optimal settings were used to demonstrate marked increase in output efficiency of vape devices (10.91%/s) compared to jet nebulisers (0.18%/s). Using these settings, two known radiolabelled drug candidates ([^{18}F]Fluticasone propionate and [^{18}F]Fleroxacin) were assessed for their respective output and stability. [^{18}F]Fluticasone propionate demonstrated good output (4.08%/s) and stability at the highest temperature setting; these promising results warrant further investigation. [^{18}F]Fleroxacin was unstable at higher temperature and required vaping at 100°C to maintain drug integrity; output was compromised and it was concluded that this drug class was unsuitable for vape delivery. A mass median aerodynamic diameter of 1 μm and comparative activity distribution of vaped radiotracers confirmed uniform dispersion within the vape liquid and the capability for deep lung delivery using vape devices.

Key Message: The sensitive and quantitative properties of fluorine-18 radiolabelling were used to validate vape devices as novel drug delivery systems. The parameters for optimal output were determined and used to demonstrate significantly improved performance compared to a jet nebuliser. Favourable output and stability were observed for a clinically relevant radiolabelled corticosteroid.

50. ENABLING PULMONARY DRUG DELIVERY WITH NANOPOROUS PARTICLES

Irès van der Zwaan[1] Pegah Nabavi[2] Adam Feiler[2,3]

[1]*Department of Pharmaceutical Biosciences and Swedeliver, Uppsala University, Husargatan 3, Uppsala, 75237, Sweden*
[2]*Nanologica, Forskargatan 20G, SE-151 36 Södertälje, Sweden*
[3]*KTH, Royal Institute Technology, Department of Chemistry, Drottning Kristinas väg, 51SE-100 44 Stockholm*

Summary: A novel pulmonary drug delivery system has been developed comprising of nanoporous, micron-sized, amorphous silica particles to encapsulate drug substances. The particle size of these

nanoporous particles (NPPs) can be tightly controlled, as can the diameter of the pores. The particles enhance the solubility of poorly soluble compounds and may also offer the potential to control the release rate of drug to the lungs. The objective of this study was to investigate the effect of particle size and pore size on drug release profiles of loaded NPPs which were aerosolized from a dry powder inhaler.

To study the effect of particle size, NPPs ranging from 2.5 μm to 5.0 μm, with identical pore sizes, were loaded with budesonide. To explore the effect of pore size, NPPs of the same size (2.2 μm), but different pore diameters (2 nm and 7 nm) were loaded with a highly insoluble novel drug candidate (CMPD-X).

A modified Andersen cascade impactor (mACI) was used to characterise the deposited particle fraction. Budesonide dissolution from the particles was studied in simulated lung fluid (SLF; Gamble's solution). The dissolution rate of budesonide was greater after being loaded in NPPs compared to budesonide particles taken from a Pulmicort® Turbuhaler®. Reducing particle size of NPPs from 5.0 μm to 2.5 μm increased the rate of dissolution of budesonide. Looking at the effect of pore size on release rate of CMPD-X, the data showed that reducing the pore diameter from 7 nm to 2 nm decreased the release rate of the drug. It is notable that regardless of the pore size, encapsulating CMPD-X into NPPs significantly increased the amount of drug released into solution. Together these results strongly indicate that the ability to control both particle size and the pore diameter of the NPPs could offer a significant formulation advantage for some drugs in development.

Key Message: Both the particle size and the pore diameter of nanoporous amorphous silica particles can be controlled and utilised to influence the rate at which encapsulated drugs are released into solution. This may offer a significant formulation advantage for some drugs intended for pulmonary delivery.

51. IN VITRO AND IN VIVO EVALUATIONS OF THE TOLERANCE OF A NEW AND INNOVATIVE ANTI-TUBERCULOSIS DRUG COMBINATION BY INHALATION

Faustine Ravon[1,2], Elena Menchi[1], Myriam Remmelink[3], Selma Chraibi[1], Véronique Fontaine[2] & Nathalie Wauthoz[1]

[1]*Unit of Pharmaceutics and Biopharmaceutics, Faculty of Pharmacy, Université Libre de Bruxelles, Boulevard du Triomphe, Brussels, 1050, Belgium*
[2]*Unit of Microbiology, Bioorganic and Macromolecular Chemistry, Faculty of Pharmacy, Université Libre de Bruxelles, Boulevard du Triomphe, Brussels, 1050, Belgium*
[3]*Department of Pathology, Hôpital Erasme, Université Libre de Bruxelles, Route de Lennik 808, Brussels, 1070, Belgium*

Summary: A drug combination, vancomycin (VAN) plus tetrahydrolipstatin (THL), has demonstrated an effective synergistic action *in vitro* against *Mycobacterium tuberculosis* (Mtb), inhibiting the growth of the bacilli as well as its resistant forms. Given the poor oral bioavailability of VAN and THL, and the tropism of tuberculosis for lungs, this combination is more suitable for administration by inhalation. To evaluate the local tolerability of this combination, bronchial cells, alveolar cells, and monocytes were exposed to different concentrations around the combination's minimal inhibitory concentration (MIC) of the drugs (i.e., 10 μg/mL for VAN and 1 μg/mL for THL). The VAN-treated group never reached the half MIC (IC_{50}), even at a concentration 80 times higher than the combination MIC. However, for THL-treated and VAN/THL-treated groups, the IC_{50} measured 30 to 50 times the combination MIC, due to the action of THL. It was demonstrated, using a lactate dehydrogenase assay, that this effect was related to a cytostatic and not a cytotoxic action. Subsequently, an *in vivo* experiment was performed at a concentration of 50 times the combination MIC, administered 3 times a week for 3 weeks on different groups of healthy mice, using an endotracheal device. Pro-inflammatory biomarkers (i.e., IL-1β, IL-6, and TNF-α) in bronchoalveolar lavage fluid remained insignificant *vs.* the negative control group, and lung histopathology did not show significant tissue damage. The VAN/THL combination at doses up to 50 times the combination MIC seems very well tolerated *in vitro* and *in vivo*; a promising result which encourages us to continue the development of an inhalation form of this combination to fight Mtb.

Key Message: The present work shows local tolerance of a potential anti-tuberculosis drug combination *in vitro* and *in vivo*. To date, this represents the first tetrahydrolipstatin study with administration by inhalation that provides the absence of cytotoxic activity and leads to multiple possibilities of use.

52. TRANSPORT OF LOCAL ANAESTHETIC LIDOCAINE ACROSS A PHARYNGEAL AIR-LIQUID INTERFACE CELL MODEL

Zara Sheikh[1], Antonella Granata[1], Dina Silva[1], Paul Young[1,3], Hui Xin Ong[1,2], Daniela Traini[1,2]

[1]*Woolcock Institute of Medical Research, 431 Glebe Point Road, Glebe NSW 2037, Australia*
[2]*Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, NSW 2109, Australia*
[3]*Macquarie Business School, Macquarie University, NSW 2109, Australia*

Summary: An *in vitro* air-liquid interface model (ALI) of human respiratory epithelial cell lines is an invaluable tool that phenotypically mimics the *in vivo* airway epithelium and is extensively used to study drug transport and predict therapeutic efficacy. Although several studies have utilized the human pharyngeal cell line Detroit 562 under ALI conditions, no studies have yet been performed to optimise the ALI culture conditions and determine whether the ALI model could be used to study drug transport. Therefore, this study aims to determine the appropriate *in vitro* ALI culture method required to establish the epithelial barrier properties of the Detroit 562 cell line and investigate drug transport of a local anaesthetic throat spray, Lidocaine. In summary, the present study indicated the suitability of the Detroit 562 cell line at a seeding density of 1.8×10^5 cells/cm^2 as a representative *in vitro* ALI cellular model to study drug transport on day 18 of the ALI culture period. Further investigations are required to characterize this cellular model by immunostaining with markers of tight junction proteins and determine differentiating features such as mucus production and response to an inflammatory stimulus.

Key Message: An *in vitro* air-liquid interface (ALI) model of the pharyngeal cell line Detroit 562 attains epithelial barrier integrity after 18 days in ALI culture, at an optimum seeding density of 1.8×10^5 cells/cm^2. This model could be used to study drug transport mechanisms and predict the therapeutic efficacy of oropharyngeal deposition of drugs and toxins.

53. FORMULATION DEVELOPMENT OF INHALABLE DACOMITINIB POLYMERIC NANOPARTICLES FOR NON-SMALL CELL LUNG CANCER TREATMENT

Druvasarika Barji, Suyash M. Patil, Nitesh K. Kunda

Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, Jamaica, NY 11439, USA

Summary: Pulmonary delivery of cancer therapeutics has a huge untapped potential for the treatment of lung cancer. Inhalable polymeric nanoparticles are an attractive strategy as they provide localized delivery of drug with minimal systemic adverse effects. In this study, Dacomitinib (DMB), a second-generation tyrosine kinase inhibitor (TKI) used in the treatment EGFR (epidermal growth factor receptor) mutant non-small cell lung cancer (NSCLC),was developed as an inhalable polymeric nanoparticle formulation. Dacomitinib has been successfully encapsulated into nanoparticles (NPs)s resulting in a size of 202 ± 32.5 nm with a PDI of 0.183 ± 0.061, and zetapotential of -19.39 ± 2.50 mV. The NPs exhibited an entrapment efficiency of $55.06 \pm 6.3\%$ and a drug loading of $27 \pm 0.01\%$. With respect to *in vitro* drug release, the DMB-NPs showed sustained drug release with cumulative release of $39.2 \pm 7.5\%$ over 5 days. Moreover, DMB-NPs demonstrated efficient lung deposition with mass median aerodynamic diameter of $3.77 \pm 0.17\ \mu$m and fine particle fraction of $80.86 \pm 1.02\%$.

Key Message: This study reported the formulation development of polymeric dacomitinib nanoparticles for NSCLC treatment with optimum particle characteristics and excellent in vitro aerosol performance

54. NASAL-PAMPA: A NOVEL IN VITRO TOOL FOR PREDICTION OF INTRANASAL DRUG PERMEABILITY

Patrícia Henriques[1,2], Joana Bicker[1,3]
Slavomíra Doktorovová[2], Ana Fortuna[1,3]

[1]Laboratory of Pharmacology, Faculty of Pharmacy, University of Coimbra, Pólo das Ciências da Saúde, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal
[2]R&D, Drug Product Development, Hovione FarmaCiencia SA, Lisbon, Portugal
[3]CIBIT/ICNAS, Coimbra Institute for Biomedical Imaging and Translational Research, University of Coimbra, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal

Summary: In nasal drug product development, biorelevant *in vitro* methodologies are vital in order to select promising compounds or formulations, potentially reducing pre-clinical and clinical trials. Permeability assays are often applied to predict drug absorption and bioavailability. For nasal delivery products, permeation models include *ex vivo* models using excised nasal mucosa and *in vitro* cell culture models. However, *ex vivo* models present high variability and cell culture models are very time consuming. The Parallel Artificial Membrane Permeability Assay (PAMPA) has emerged as a high throughput screening tool to evaluate drug permeability, and it has been applied to several barriers such as the intestine, skin or blood-brain-barrier. Herein, a new PAMPA model was developed and optimized to predict nasal permeability, using a biorelevant donor medium containing mucin. The apparent permeability (P_{app}) of 15 reference compounds was assessed in six different experimental conditions. The model with 0.5% (w/v) mucin in the donor compartment and 2% (w/v) phosphatidylcholine in the lipid membrane correctly distinguished high and low permeable compounds, with no false positives or negatives. In addition, it exhibited the highest correlation with permeation across human nasal epithelial RPMI 2650 cells ($R^2 = 0.71$). Overall, the optimized PAMPA model was reproducible, predictive and inexpensive, showing to be a promising non-cell based and biorelevant *in vitro* tool that could be applied in an early screening stages of new nasal drug delivery products.

Key Message: A new nasal-PAMPA model with 0.5% (w/v) mucin on donor compartment and 2% (w/v) phosphatidylcholine in lipid membrane can differentiate high and low permeable compounds for nasal delivery and shows to be a promising predictive and high throughput tool for assessment of intranasal drug permeability for application in early phase screening studies.

55. SURFACE ACOUSTIC WAVE NEBULISATION FOR TARGETED INHALATION DRUG DELIVERY TO CENTRAL AND PERIPHERAL AIRWAYS

Christian Witte[1], Elijah Nazarzadeh[1], John Pritchard[1], Julien Reboud[2], Jonathan M. Cooper[2]

[1]Acu-Flow Limited, Rankine Building, Oakfield Avenue, Glasgow, G12 8LT, UK
[2]University of Glasgow, Rankine Building, Oakfield Avenue, Glasgow, G12 8LT, UK

Summary: This work presents surface acoustic waves (SAW) as a technology for controlled aerosolisation of formulations with a wide range of physical properties, including viscous solutions and those with low surface tension that are often challenging to deliver. The acoustic waves were coupled into microstructured arrays of cavities with sizes in the range of 100s of micrometers to nebulise liquids. The aerosols generated by the nebuliser engine were characterised using an Anderson Cascade Impactor. The mass median aerodynamic diameter (MMAD) was consistently $<2\mu$m for model drug systems, ranging from 1% sodium chloride to 50% ethanol, whilst it was ca. 1.3μm for antibiotic drug formulations of Tobramycin and Amikacin. These results demonstrate significant reduction in the size of the droplets in the aerosol compared to previous technologies. This suggests a route for targeted delivery of inhalable antibiotic drugs to the central and peripheral airways, potentially avoiding side effects associated with intravenous or oral application, as well as reducing drug waste and the risk of development of drug resistant bacteria often linked to other modes of delivery.

Key Message: Surface Acoustic Waves coupled into an array of microstructured cavities can aerosolise a wide range of formulations with a high respiratory fraction, enabling targeted delivery of inhalable antibiotic to the peripheral airways.

56. THE EVOLUTION OF UNSTEADY FLOW FROM DRY POWDER INHALERS

Vishal Chaugule[1], Suzanna Olofsson[1], Larissa Gomes dos Reis[2], David F Fletcher[3], Paul M Young[2,4], Daniela Traini[2,5] & Julio Soria[1]

[1]Laboratory for Turbulence Research in Aerospace and Combustion (LTRAC), Department of Mechanical and Aerospace Engineering, Monash University, Clayton Campus, Melbourne, VIC 3800, Australia
[2]Respiratory Technology, Woolcock Institute of Medical Research, Sydney, NSW 2037, Australia
[3]School of Chemical and Biomolecular Engineering, The University of Sydney, Sydney, NSW 2006, Australia
[4]Department of Marketing, Macquarie Business School, Macquarie University, NSW 2109, Australia
[5]Department of Biomedical Sciences, Faculty of Medicine, Health and Human Sciences, Macquarie University, NSW 2109, Australia

Summary: The time-dependent behaviour of the aerosolized inhalation flow produced from a dry powder inhaler (DPI) significantly affects the dynamics of aerosol generation. A characterisation of such an unsteady DPI flow is therefore important to better understand the device aerosol performance. The unsteady flow emerging from two analogue DPI models, one with and the other without a grid, has been

examined. These models are a modified form of an original design with two tangential inlets. Particle image velocimetry was used to measure the spatio-temporal DPI fluid flow velocity field. These measurements were performed using a piston-driven water-based experiment under geometrically and dynamically similar conditions to the original DPI model operating in air, and were taken in a longitudinal plane outside the DPI mouthpiece. The unsteady inhalation flow through the DPI is simulated by a forward piston-stroke pushing fluid through the DPI model. The ensemble-averaged velocity vector-fields for the two models show the spatio-temporal evolution of the emerging DPI flow. An axially-recirculating and laterally-spreading jet flow arising from the model without the grid is found to develop. These flow features occur due to high flow-swirl and lead to drug losses due to particle retention in the device and deposition due to impaction in the mouth-throat region. The jet flow emerging from the model with the grid is found to spread less, but has a large central reverse-flow region that persists for a considerable time of the flow duration.

Key Message: The spatio-temporal evolution of the flow-field emerging from two DPI models outline the formation and growth of axially-recirculating and lateral-spreading flow regions. These affect the device aerosol performance, with the reverse flow leading to drug particle retention in the device, and the lateral-spreading results in impaction losses in the mouth-throat region.

57. ASSESSMENT OF AEROSOL DRUG DELIVERY DURING THE ESCALATION OF TREATMENT FOR A SIMULATED COVID-19 ADULT PATIENT

Ronan MacLoughlin, Marc Mac Giolla Eain, Andrew O'Sullivan, Leanne Reilly, Keith Hurney, Mary Joyce[1],

[1]Aerogen Ltd., Galway Business Park, Dangan, Galway, H91 HE94, Ireland

Summary: The effect of the various COVID-19 clinical interventions on aerosol delivery is not well known. This study investigated the use of a vibrating mesh nebuliser to deliver aerosolised drugs during mouthpiece-mediated aerosol drug delivery, high flow nasal therapy and invasive mechanical ventilation employing a low tidal volume ventilation strategy. Simulated adult healthy and mild adult COVID-19 breathing patterns were used for spontaneous breathing assessments. A mechanical ventilator delivered standard and low tidal volume ventilation parameters.

The results presented represent the percentage drug delivered to a simulated healthy adult and mild adult COVID-19 patient during concurrent aerosol therapy during these interventions. The highest delivered drug dose was measured during mouthpiece-mediated aerosol therapy with a result of 57.93 % ± 1.05 % for mild COVID-19, 56.64 % ± 2.94 % for healthy, as a comparator.

Use of HFNT resulted in the lowest percentage drug delivered (2.33 % ± 0.99 % for 30 LPM; 1.80 % ± 0.61 % for 60 LPM), with no significant difference between the flow rates ($p = 0.6220$). For mechanical ventilation, there was a significant difference in adopting a LTV ventilation strategy (13.66 % ± 0.75 %) in comparison to a standard ventilation (30.34 % ± 0.27 %) ($p < 0.0001$).

It can be concluded that the choice of clinical intervention in the oxygenation and ventilatory support of the COVID-19 patient influences aerosol delivery to the lung. This variability may be significant and therefore should be noted in the design of dosing strategies, and de-risking of clinical trial programs.

Key Message: The choice of clinical intervention in the oxygenation and ventilatory support of the COVID-19 patient influences aerosol delivery to the lung. This variability may be significant and therefore should be noted in the design of dosing strategies, and de-risking of clinical trial programs.

58. DEVELOPMENT OF A PROTOTYPE OF AN AEROSOLIZATION DEVICE FOR DRY POWDERS TO IMPROVE IN VITRO CELL-BASED ASSAYS IN THE CONTEXT OF LUNG DELIVERY

Jorge F. Pontes[1,2], Hermínio P. Diogo[3], Eusébio Conceição[4], Flávia Musacchio[1], Rui M. Borges dos Santos[1,4] & Ana Grenha[1,4]

[1]Centre for Marine Sciences, Universidade do Algarve, Campus de Gambelas, Faro, 8005-139, Portugal
[2]Centre for Biomedical Research, Universidade do Algarve, Campus de Gambelas, Faro, 8005-139, Portugal
[3]University of Lisbon, Instituto Superior Técnico, Centro de Química Estrutural, Av. Rovisco Pais, 1049-001 Lisbon, Portugal
[4]Faculdade de Ciências e Tecnologia, Universidade do Algarve, Campus Gambelas, Faro, 8005-139, Portugal

Summary: The lung has been, for the past years, subject of intense research for local and systemic drug delivery approaches. However, robust correlations between *in vitro* and *in vivo* results are often impaired, as *in vitro* experiments frequently have limitations mimicking lung conditions, especially when involving cell-based studies. This work proposes a 3D-printed device for aerosolization of dry powders over cells in culture, thus better resembling the conditions of aerosolization occurring *in vivo*. The proposed device comprises two parts, the weighing head, and the main body. Dry powders are weighed in the weighing head, which is then sealed to the main body. Next, compressed air is injected into the device, dragging the powder onto a plate, which fits the bottom of the main body. The plate is a suitable surface for cell culture. Dry powders (polysaccharide-based microparticles) were tested using the device, leading to an aerosolization yield up to 51%, which was observed to depend on the tested dry powder. The dry powder deposition profile is currently being evaluated using a Quartz-Crystal Microbalance, which replaces the plate at the bottom of the device's main body. These experiments entail a more precise determination of the mass of aerosolized powders by analysing the differences in the vibration frequencies of a quartz crystal, thus allowing to assess the deposition profile. Although preliminary, the results show that the developed device may comprise an affordable solution for *in vitro* testing of dry powders when aerosolization over a surface is required.

Key Message: The developed prototype of an aerosolization device can homogenously disperse dry powders over cell layers, comprising a cheaper alternative for *in vitro* cell-based experiments that allows better resembling the conditions of powder aerosolization.