JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY
Volume 27, Number 4, 2014

Pp. A-1–A-27
DOI: 10.1089/jamp.2014.ab01.abstracts

Abstracts from The Aerosol Society Drug Delivery to the Lungs 24

Edinburgh International Conference Centre
Edinburgh, Scotland, UK
December 11–13, 2013

Abstracts: Drug Delivery to the Lungs 24

1. COMPLETE THE CYCLE – GSK'S INHALER RECYCLING PROGRAMME

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Summary

GlaxoSmithKline has developed an inhaler recycling and recovery scheme which is simple and easy for pharmacies to participate in, and enables patients to reduce the harmful impact associated with landfill disposal. It provides additional opportunities for pharmacists to interact with patients and creates benefits for pharmacies beyond recycling. Through Complete the Cycle, GSK will recycle or recover every respiratory inhaler collected by participating pharmacies, including those inhalers manufactured by other companies. The paper will outline the challenges and opportunities presented in operating an inhaler recycling scheme.

2. INVESTIGATION OF NOZZLE DESIGNS AND MATERIAL ON THE ELECTROSTATIC CHARGE OF PRESSURISED METERED DOSE INHALER

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Summary

Background: Electrostatic charge plays an important role in particle deposition in pressurized metered dose inhaler (pMDI) and is influenced by factors, such as chemical/physical properties of the formulation and device materials. Charges can accumulate at the sharp edges of the pMDI actuator, leading to electrostatic discharge to the surrounding environment and causing changes in inhalation aerosol charge profile. In this study the influence of different nozzle designs, using conducting and insulating actuator materials, on pMDI aerosols performance was investigated.

Methods: Two actuator materials (aluminium and polyethylene terephthalate), each with four types of nozzle designs (flat, curved flat, cone and curved cone) were tested using the electrical low-pressure impactor (ELPI) for the determination of their electrostatic charge profiles. Beclomethasone (BDP) pMDI solution was chosen as model formulation and drug deposition was analyzed and assayed using high performance liquid chromatography (HPLC).

Results: Curved nozzle designs for the insulating PET actuator significantly influenced charge profiles ($-$ve polarity to $+$ve polarity) and drug deposition (ANOVA, $p < 0.05$) compared with the metal aluminium actuator. These results are probably due to the change of plume geometry imparted by the curved edge nozzle design. Aluminium flat nozzle shown significantly higher electronegative charge ($-249.45\text{pC} \pm 77.22$) and higher induction port deposition (66.78 % of total ex-valve dose), indicating particle deposition is influenced by the electrostatic charge magnitude.

Conclusion: The property of the actuator materials and nozzle designs could both influence aerosol electrostatic charges suggesting that, by choosing different nozzle design and actuator materials combination, drug deposition pattern for pMDI formulations could be altered.

3. RAMAN-BASED ANALYSIS OF DISPERSED VERSUS AGGREGATED DRUG PARTICLES IN MDI FORMULATIONS FOR CHEMICALLY-SPECIFIC SIZING AND POLYMORPHIC PURITY ASSESSMENT

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Background: Inhalation drug testing as it relates to dose delivery profile and drug particle size distribution (PSD) is essential for establishing the desired therapeutic effect of inhalable products. Physical properties of the drug molecules, particularly PSD and extend of drug particles aggregates may be assessed by Raman Chemical Imaging (RCI) more accurately then by microscopy or cascade impaction analysis alone due to the subjectivity and lack of chemical specificity of these methods. For inhalation route of administration, efficacy of the drug also relates to its polymorph stability and purity since it directly affects adhesion-cohesion interaction of the drug molecules to an excipient and or carrier. Raman-based imaging approach is shown to be advantageous to assess (BA)/(BE) of OINDPs and investigate less stable forms of polymorphs for which other methods are not suitable.

Methods: In this study, RCI was used to investigate the fluticasone propionate particle size distribution, and access degree of drug particle aggregation in a commercial MDI, Flixotide. Assessment of free-standing and aggregated drug particles was done by visual inspection of Raman-detected

drug particles as it relates the spatial location/Raman signal intensity of all identified fluticasone particles on a the brightfield and Raman Chemical fusion Images.

Results: By using Raman imaging it is possible to identify foreign particulates in the formulations and obtain spectrally and spatially resolved images of each particle for accurate particle size determination and recognition of aggregated versus stand-alone particles. Developed analytical method allowed analysis of different chemical species or polymorphic/hydrate forms of the same chemical within single particle or aggregate for identification of polymorphic impurity/unwanted phase transition.

Conclusions: Raman Chemical Imaging was used to confirm polymorphic purity and differentiate stand-alone from co-associated particles to assess dispersion profile and agglomeration effect on product aerosolation performance.

4. THE FORMULATION OF A NOVEL MACROLIDE SOLUTION PRESSURISED METERED DOSE INHALER: THE USE OF CLARITHROMYCIN AS AN ANTI-INFLAMMATORY FOR BRONCHIECTASIS THERAPY

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Summary

Background: Several studies have corroborated that clarithromycin, a macrolide antibiotic, has anti-inflammatory effects in respiratory diseases. Currently, 250 mg of oral clarithromycin is prescribed three times a week to reduce inflammation in asthma, bronchiectasis and chronic obstructive pulmonary disease. To date, no studies have focused on the local administration of clarithromycin.

Methods: The formulation and characterisation of a clarithromycin pressurised metered dose inhaler (pMDI) solutions was investigated. The solubility of the drug in propellant/co-solvent mixtures was measured using an in *in situ* solubility apparatus. Particle size distribution was investigated using the Andersen cascade impactor. Calu-3 sub bronchial epithelial cell line in the air interface culture model was used to further study the effectiveness of the formulation in terms of toxicity, barrier integrity and inhibitory effects on inflammation and mucus secretion.

Results: Clarithromycin pMDI formulation containing 10% ethanol/HFA was chosen for further aerosol deposition studies. Fine particle fraction (FPF), mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were $47.15 \pm 2.91\%$, $1.58 \pm 0.07\%$ and $1.71 \pm 0.03\%$, respectively. Particle deposition on the surface of Calu-3 using a modified Anderson cascade impactor, where the impaction plate was modified to accommodate up to eight Snapwells, showed no significant effect on barrier integrity, but resulted in a significant decrease in mucus secretion after 3 days in culture.

Conclusion: The novel clarithromycin solution pMDI was formulated and had suitable aerosol properties for lung delivery. This formulation demonstrated to be non-toxic at the administered doses and had *in vitro* inhibitory effects on mucus secretion of Calu-3. Further investigations on the anti-inflammatory activity are ongoing.

5. UNDERSTANDING THE MIXING BEHAVIOR OF MECHANICALLY MODIFIED GLASS BEADS AS MODEL CARRIERS IN DPIs AND SALBUTAMOL SULPHATE

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Summary

The aim of this work is to understand the mixing behaviour of mechanically modified glass beads as model carriers in DPIs and spray dried salbutamol sulphate as model active pharmaceutical ingredient (API) particles. Regardless of what glass beads were used a 100% surface coverage could not be achieved although the amount of API weighed in was calculated for a 100% surface coverage. The actual surface coverage reached for the mechanically modified glass beads was about 75% compared to a 32% actual surface coverage for the untreated glass beads. By preparing adhesive mixtures with different calculated surface coverage, the calculated coverage and the actual coverage could be correlated for all the distinct glass beads used and linear equations with different slopes could be set. Based on these correlations comparable mixtures with $30\% \pm 5\%$ actual surface coverage could be prepared. The evaluation of the fine particle fractions (FPF) showed that the FPF is varying for the differently modified glass beads and dependent on the surface characteristics of the glass beads. For mechanically modified glass beads the FPF can be correlated with the surface roughness and the specific surface area of the glass beads. The higher the surface roughness and the higher the specific surface area of the glass beads the higher the FPF.

This study shows that by understanding the mixing behaviour of mechanically modified glass beads, comparable mixtures with defined actual surface coverage can be prepared. As a result the performance of the differently modified glass beads can be compared.

6. AERODYNAMIC CHARACTERISATION OF PLGA NANOPARTICULATE DRY POWDER FORMULATION FOR VACCINE DELIVERY VIA THE RESPIRATORY TRACT

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Polymeric nanoparticles offer a possibility as particulate carrier system for vaccines which can be administered to the respiratory tract. Nanoparticles were produced from PLGA by double emulsion technique and spray dried after solvent evaporation. The antigen, in this case ovalbumin as model antigen, was encapsulated inside the nanoparticles. PVA

was used in order to stabilise the produced nanoparticles. Furthermore PVA acts as a bulking agent during spray drying; hence no further additives were necessary. Before spray-drying the particles have a size of 250 nm and a narrow size distribution. The spray-drying process embeds the antigen-carrying nanoparticles into PVA microparticles which can easily be redispersed to nanoparticles. Laser diffraction measurements of the spray dried powder showed an average particle size of 2.3 μm.

The obtained dry powder was filled into HPMC capsules and the aerodynamic properties were determined with Next Generation Pharmaceutical Impactor (NGI) using the Unihaler, a novel capsule-based inhaler. The samples were analysed for ovalbumin content by BCA assay and fine particle fraction (FPF) as well as MMAD were calculated. FPF was about 50% of the loaded dose and mass median aerodynamic diameter (MMAD) was 3.1 μm. Furthermore the emitted dose was investigated with a dose unit sampling apparatus for DPIs according to USP Apparatus B and was found to be 75% for the tested formulation utilising the Unihaler. The investigations of the spray dried powder produced by double emulsion technique showed that the powder is suitable for an administration via the respiratory tract. Moreover, the Unihaler can disperse the powder very well, but emitted dose may be capable of further optimisation.

7. DEVELOPMENT AND *IN VITRO* TESTING OF A NEW HIGH EFFICIENCY DRY POWDER INHALER FOR CARRIER-FREE FORMULATIONS

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Background: Current DPIs on the market have fine particle fractions (FPF) in the range of 10–70%, produce high mouth-throat (MT) depositional losses of approximately 30–95%, and have relatively low and variable lung delivery efficiencies. A high efficiency dry powder inhaler (DPI) was developed and tested for use with carrier-free formulations across a range of different *in vitro* inhalation flow rates.

Methods: The performance of the new design was investigated and reported in terms of aerosolization characteristics. The new design oriented the capsule chamber (CC) at an angle of 90 degrees to the main flow passage, which contained a 3D rod array for aerosol deaggregation.

Results: Orienting the CC at 90° to the mouthpiece produced an albuterol sulfate emitted dose (ED) of 73.4%, fine particle fractions (FPFs) less than 5 μm and 1 μm of 95.1% and 31.4%, respectively, and a MMAD of 1.5 μm when tested at a flow rate of 45LPM. The variability associated with both ED and deaggregation was low with the CC_{90}-3D design when tested between 31.8 to 55.1 LPM, respectively. There was no significant change in emitted dose across the range of flow rates. FPF changes of approximately 1% in value and MMAD changes of approximately 0.1 μm in value, were observed.

Conclusions: The new inhaler produced an extremely high quality aerosol with little sensitivity to flow rate and is expected to deliver approximately 95% of the ED to the lungs.

8. AN ASSESSMENT OF THE COMPARATIVE EFFICIENCY OF ABBREVIATED VERSUS FULL RESOLUTION CASCADE IMPACTOR MEASUREMENTS: A SURVEY OF EUROPEAN PHARMACEUTICAL AEROSOL GROUP (EPAG) MEMBERS

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Summary

The Impactor Sub-Team of EPAG has conducted a survey amongst its member organizations to assess quantitatively the magnitude of time savings that are being realized with Abbreviated Impactor Measurement (AIM) cascade impactors (CIs) compared with full resolution systems in their own day-to-day operations. Eight different organizations responded to the survey, with information relating to the laboratory assessment of an assortment of pressurized metered dose inhalers (pMDIs) with and without valved holding chamber (VHC) add-on devices and dry powder inhalers (DPIs). Nebulizing systems were not represented. The magnitude of efficiency gains linked to the use of AIM-based methodologies was very dependent on the organization concerned, resulting in large variability in the aggregated data. Nevertheless, the efficiency gains per particle size distribution measurement using AIM-based methods were estimated to be 67% and 39% with and without HPLC assay time included respectively. It was therefore concluded that there are tangible gains to be made in overall CI method efficiency if an AIM-based option is introduced. This survey should be repeated in 5-years time, when it is to be hoped that more respondents, especially those evaluating OIP formats other than DPIs can be encouraged to participate.

9. CONTROL AND REDUCTION OF FOREIGN PARTICLES IN THE MANUFACTURING PROCESS OF A DRY POWDER INHALER PRODUCT – APPLYING A QUALITY BY DESIGN STRATEGY BASED ON IPAC-RS RECOMMENDATIONS

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Summary

The Food and Drug Administration (FDA) addresses testing for foreign particles in inhalational drug products. A Quality by Design (QbD) approach based on IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science) recommendations was used to gain a good understanding of particulate contamination over our entire inhaler production process. The number of foreign particles in several drug substance batches before and after a change in manufacturing was enumerated by light obscuration. This was done in order to monitor potential influences on foreign particulate quality and for being in a position to take measures before receiving critical findings in the drug product. Therefore, drug substance was weighed into specially cleaned laboratory bottles and dissolved in a water/acetonitrile solvent.

The results revealed that the drug substance contained approximately four times as many foreign particles after the change in production when compared to those before the change. Based on these results, we decided to implement an additional filtration step to the production process of the drug substance. As a result, the amount of foreign particles in the drug substance batches dropped to their previous levels. This proactive QbD approach provided us with an effective tool to not only prevent a negative impact from foreign particles on the drug product quality, but to also ensure patient safety.

10. A DESIGN OF EXPERIMENTS STUDY APPLIED TO A MECHANOFUSION PROCESS FOR SURFACE MODIFICATION OF SALBUTAMOL SULPHATE

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Surface modification of drugs for inhalation provides an approach to improve powder dispersibility and reduce intrinsic cohesion as micronised drugs tend to agglomerate. The intention of this study is to change interparticulate forces and improve the aerosolisation behaviour. The drug surface can be modified by using force control agents (FCAs). Mechanofusion systems use the applied mechanical forces for dry particle coating. In this study the picobond® system with AMS module was used to alter the surface of salbutamol sulphate (SBS) with different concentrations of the additive, magnesium stearate (Mgst). A design of experiments (DoE) was applied to evaluate the influencing parameters on the powder de-agglomeration which was investigated using a Next Generation Impactor (NGI). The fine particle fraction (FPF) ($\leq 5\,\mu$m) was calculated and defined as response factor of the three factor central composite design (CCD) which is a standard response surface methodology (RSM). It was possible to find a significant model (p-value < 0.05) for the FPF. Furthermore, it could be shown that the rotational speed and the interaction between process time and Mgst concentration have a significant influence on the FPF. For higher excipient concentrations it is better to use a longer process time and vice versa. In this study the mechanofusion parameters are systematically investigated to obtain an improved process understanding.

11. PREPARATION AND CHARACTERIZATION OF CRYSTALLINE, SEMI-CRYSTALLINE AND FULLY AMORPHOUS POWDERS OF HYDROPHILIC AND LIPOPHILIC ACTIVE PHARMACEUTICAL INGREDIENTS

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Summary

Background: It is well-known that standard pharmaceutical operations may lead to structural changes, crystal defects and amorphous regions of solid particles. Especially operations like milling, blending and even sieving generate these effects to excipients and active pharmaceutical ingredients (APIs). These disorders induce re-crystallization and particle size change which have a huge influence on drug delivery and product stability. In this study a crystalline hydrophilic and lipophilic API is used for the preparation of semi-crystalline and fully amorphous samples and analysed by a variety of different analytical methods.

Methods: A ball-mill and a spray dryer were used to create fully amorphous samples. The study target was to find out differences between the production methods and differences in the behaviour of the contrasting APIs. Furthermore the fully amorphous powders were used to quantify amorphous parts which were generated by micronization processes and blending.

Results: Both production processes (BM/SD) resulted in fully amorphous products and it was possible to characterize successfully crystalline, semi-crystalline and amorphous powders with different methods. In this analysis the completely amorphous ball-milled API was used for the preparation of a calibration curve with the help of the DVS. Because of this reason lower amorphous contents were found in micronized powders and in mixing tests with glass beads. It was possible to calculate amorphous parts between 0.55% and 5.04% depending on API and process method.

Conclusions: This study has shown that unit operations, such as blending, milling or micronization, may have a huge influence on physical state. Because of the resulting low sensitivity of the DVS method (water) for the hydrophobic batch there has to be established a DVS sorption method with organic solvent.

12. THE INFLUENCE OF SEMI AND NON-VOLATILE COMPONENTS ON THE MORPHOLOGY OF PARTICLES GENERATED FROM SOLUTION-BASED PRESSURIZED METERED-DOSE INHALERS

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Summary

Background: Particle formation mechanisms and aerosol performance of solution-based pressurized metered dose inhalers (pMDIs) are dramatically changed when ethanol is introduced in the formulation. The current study is to investigate the effect of ethanol on particle formation and aerosol performance of solution pMDIs using different pharmaceutical compounds.

Methods: The aerosol performance of solution pMDIs containing beclomethasone dipropionate, fluticasone propionate and caffeine, with different ethanol concentrations and doses was evaluated using aerosol cascade impaction. The surface and internal structures of the particles were examined using Scanning Electron Microscopy (SEM) and Focus Ion Beam–Scanning Electron Microscopy (FIB-SEM).

Results: The aerodynamic performance of the experimental formulations showed a significant reduction as the ethanol concentration in a formulation was increased.

Particles produced from two corticosteroid formulations were amorphous with two different types of morphology – smooth surface with a solid core and coral-like with porous internal structure. Caffeine particles were crystalline with elongated morphological feature.

Conclusion: Due to the difference in ethanol concentration in emitted droplets, residual particles from solution pMDIs may have distinct drying process: droplets with less ethanol will be dried during the propellant/ethanol co-evaporation period and ethanol-abundant droplets will undergo an extra ethanol condensation stage after depletion of propellant.

13. A NOVEL APPROACH TO DEVELOP HIGH DOSE DRUG ALONE INHALER

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Backgrounds: The development of high dose inhalers is becoming obvious with the emerging use of inhalation route for the delivery of antibiotics and vaccines. The purpose of this study was to evaluate the mechanical dry coating process to develop drug alone formulation of high dose delivery capacity.

Methods: Fine inhalable grade lactose was dry coated with 1% magnesium stearate (w/w), and the powder was dispersed from two devices, the Rotahaler® (RH) and Monodose Inhaler® (MI) at three flow rates of 60 $L min^{-1}$ with dose loads of 10, 25 and 40 mg. The primary particle size distributions, tapped density and work of cohesion were determined by laser diffraction method, tapped density apparatus and inverse gas chromatography, respectively.

Results: Fine particle dose (FPD, amount of drug that can reach in lower respiratory tract) displayed a marked increase after mechanofusion. The maximum FPD of 14 mg was obtained when 40 mg dose was dispersed from Monodose Inhaler at 60 L/min. No significant difference was observed between the untreated and mechanofused powder ($P > 0.05$). After mechanofusion, the poured and tapped densities as well as the packing fraction increased while the work of cohesion decreased.

Conclusions: Although further studies are required, these preliminary findings indicate that mechanical dry coating with magnesium stearate is promising in developing dry powder inhalers for high dose delivery efficiency.

14. VARIABILITY IN PARTICLE SIZE OF CURRENT COMMERCIALLY AVAILABLE NEBULIZERS

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Publications from the 1990s reported high variability in the particle size and respirable fraction of aerosol from nebulizers.[1,2] In recent years, many innovations in nebulizer design have occurred, intended to reduce treatment times, improve respirable doses, and reduce variability.[3–5] In this study, a range of nebulizers with different designs were characterized in terms of mass median diameter (MMD) and fine particle fraction (FPF; % of particles $< 5\,\mu m$) using laser diffraction. Nine nebulizers were selected for testing: conventional jet nebulizers (Salter 8900 Series, Salter Labs, Arvin, CA, USA; SideStream, Respironics Respiratory Drug Delivery (UK) Ltd, Chichester, UK); breath-enhanced jet nebulizers (LC Plus, PARI GmbH, Starnberg, Germany; LC Sprint, PARI GmbH; SideStream Plus, Respironics Respiratory Drug Delivery (UK) Ltd); a breath-activated jet nebulizer (AeroEclipse II, Monaghan Medical Corp., Plattsburgh, NY, USA); non-breath-enhanced vibrating mesh devices (eFlow rapid, PARI GmbH; MicroAir U22, OMRON Healthcare, Kyoto, Japan); and a breath-activated and monitoring mesh nebulizer (I-neb Adaptive Aerosol Delivery System, Respironics Respiratory Drug Delivery (UK) Ltd, Chichester, UK). It was concluded that there remains a high variability in the MMD and FPF of aerosols produced from nebulizers, which has not changed significantly since the 1990s, despite new developments. Selection of a nebulizer by its performance characteristics, including MMD and FPF, is as important now as in the past. Variability in nebulizer performance, in terms of particle size, may have clinical implications.[6]

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15. EMITTED DOSE OF AEROECLIPSE II AND SIDESTREAM PLUS NEBULIZERS WHEN USING PEDIATRIC APPLICATIONS WITH A FACEMASK

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Previous studies compared delivered dose results from a range of nebulizers; one finding was that the AeroEclipse II breath-activated nebulizer (Monaghan Medical Corp., Plattsburgh, NY, USA) produced a higher dose than other jet nebulizers.[1,2,3] These studies were performed with simulated adult breathing patterns and the AeroEclipse II nebulizer was used in breath-activated mode. For pediatric and low-flow patient breathing patterns it is required that the nebulizer is switched to continuous mode, as the inhalation flow is insufficient to trigger the breath activation of aerosol generation. In this study we investigated the output of the AeroEclipse II nebulizer in continuous mode, and compared it to a reference breath-enhanced nebulizer, the SideStream Plus nebulizer (Respironics Respiratory Drug Delivery (UK) Ltd, Chichester, UK). The nebulizers were tested with a pediatric facemask (small, disposable AeroEclipse II mask, Monaghan Medical Corp.) and attached to an ASL 5000

breathing simulator (IngMar Medical Ltd, Pittsburgh, PA, USA), which was programmed to reproduce a simulated pediatric breathing pattern (tidal volume=151 mL, breaths per minute=25, inhalation:exhalation ratio=1:1). It was found that, in breath-activated mode, the inhalation flow was, as expected, unable to produce aerosol when a small, disposable AeroEclipse II facemask was used. When used in continuous mode, the AeroEclipse II nebulizer produced a lower emitted dose of salbutamol sulphate (5 mg/2.5 mL, Salamol Steri-Neb, IVAX Pharmaceuticals, West Yorkshire, UK), compared to the breath-enhanced SideStream Plus nebulizer.

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16. ITERATIVE MATHEMATICAL APPROACH FOR UNDERSTANDING DEAGGLOMERATION BEHAVIOUR OF MICRONIZED COHESIVE POWDER IN FORMULATIONS

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Abstract

Understanding deagglomeration of cohesive particles is a key component in formulating dry powder inhalers. Coarse carriers are added as diluents and to aid powder handling, and the addition of fine carrier fractions aid the aerosolization of cohesive drug particles. However, this leads to different deagglomeration mechanisms upon aerosolization. The aim of the project was to suggest an appropriate mathematical approach which defines parameters to characterize aerosolization behaviour of cohesive micronized particles alone and in combination of different grade of lactose. Salbutamol sulphate (SS) and salmeterol xinafoate (SX) were chosen as adhesively and cohesively balanced particles when formulated with lactose carriers, respectively. The drugs were blended separately with either fine lactose (FL), coarse lactose (CL) or combination of both in ratio 1:4:63.5, respectively. Laser diffraction using both dry and liquid dispersion systems was employed to characterize the powder population median particle size (i.e. Dv_{50}) and the % volume of particles below 5 μm. The deagglomeration of micronized materials followed an asymptotic mono-exponential relationship analogous to a Johnson-Mehl-Avrami-Kolmogorov equation (with positive asymptote '*m*' and deagglomeration constant '*k*'). However, when the coarse lactose was added, the relationship fitted a bi-exponential equation showing an easily and a poorly dispersed fraction. For both drugs, the extent of deagglomeration was doubled by the addition of FL to CL ($63.76 \pm 2.85\%$ and $33.62 \pm 1.14\%$ for SS:FL:CL and SS:CL, respectively) and SX:FL:CL showed the highest ease of the deagglomeration (2.61 ± 0.23). Based on the formulation studied, the two approaches could be used to understand the deagglomeration behaviour of cohesive particles in combination with lactose or alone.

17. SMOKING BEHAVIOUR SYSTEM; METHODOLOGY FOR VALIDATION

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Properties such as inhalation frequency, effort, duration, flow, volume and breath hold are key variables to determine the fate of aerosols from pharmaceutical inhalers, nebulisers and smoking articles. Population lung physiology and function are also diverse. The Smoking Behaviour System (SBS) has been developed to measure flow and duration characteristics of typical smoking cycles, which typically consist of puffing, mouth hold, post puff inhalation, breath hold and exhalation. The SBS is a novel system with regards to its capability to capture the complete smoking cycle. It comprises a head that measures the puffing topography and optical obscuration from puffed particles and a heated second head that measures the respiratory profile and optical obscuration from exhaled particles. The system was calibrated for flow, and validated in terms of system to system and day to day variation for volume and optical obscuration measurements. The puffing and respiratory heads have been tested to operate between flow rates of 0–7 $L.min^{-1}$ ($\pm 2\%$), and 0–50 $L.min^{-1}$ ($\pm 5\%$) respectively and met this specification on testing. These flow rates are typically encountered during the human smoking cycle. The optical obscuration validation measurements showed no significant difference between units across the five days that they were tested. The results provide confidence in the robustness of the system for use in field studies. These data will be presented and discussed in addition to the characterisation of the complete smoking cycle using the SBS.

18. THE INFLUENCE OF STORAGE CONDITIONS ON THE DE-AGGLOMERATION BEHAVIOR OF INHALATION POWDERS CONTAINING AMORPHOUS LACTOSE

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Micronized drugs, as used in dry powder inhaler formulations, are very cohesive. For that reason larger carrier particles, commonly α-lactose-monohydrate, are added to improve the de-agglomeration of the powders during inhalation. Different lactose qualities will result in a varying deagglomeration behavior. Beside the state of surface, the particle size and the surface area it is assumed that amorphous structures may have an influence on the powder performance. Such amorphous parts in the carrier lactose can be brought in during processing the lactose.

In this study the influence of added ball milled amorphous lactose to powder blends containing budesonide and salbutamol sulphate in different concentrations on the deagglomeration behavior was investigated. The fine particle fraction was investigated after storage at 45% and 75% RH. The fine particle fraction was lower when storing the powders at 75% RH. It could be observed, that the humidity had a greater influence on the powder containing the hydrophilic salbutamol sulphate. For all powders an in-

crease in the fine particle fraction could be observed when adding 5% milled amorphous lactose. This effect was also greater for the powder blends containing salbutamol sulphate than for the blends with budesonide. A higher concentration of salbutamol sulphate leads to a higher fine particle fraction, for both, the powder blend with 5% amorphous lactose and the blend without amorphous content. In summary, adding milled amorphous lactose increases the fine particle fraction of the powder. The differences are greater for the hydrophilic salbutamol sulphate and also the storage conditions seem to be more important for the hydrophilic drug.

19. USING HUMAN FACTORS GUIDANCE AND USER RESEARCH TO INFORM THE DESIGN OF AN INNOVATIVE NASAL MDI

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This is a case study of 3M's interpretation of the FDA Human Factors Medical Device Design Draft Guidance, in the development of a Nasal MDI for allergic rhinitis. The regulatory environment has evolved to ensure marketed products for respiratory therapy are as safe and effective as possible. This has resulted in considerable advances in understanding of the user, their environment when using the product, and the medical device (combination product) interface. The drive behind recent requirements has not come solely from the understanding of the patient's therapeutic needs, but also from consideration of other products they use in their daily lives. Many companies that develop non-medical consumer products have enhanced their device interfaces to account for increased human factors awareness. 3M has incorporated Human Factors considerations as directed by FDA Guidance, backed up by multi-stage Human Factors research with users, in developing its Nasal MDI device. Significant learning has been accumulated, which will be utilized in future device and product development across the MDI platform. The project highlighted the need to plan for user studies at several stages of the product design and development process. Complying with Human Factors Guidance will not only ensure that products are safe and effective, but ultimately will aid compliance and drive patient preference.

20. REVISITING HYGROSCOPIC GROWTH OF NEBULIZED PHARMACEUTICS DURING INHALATION: A NOVEL STRATEGY TO USE SINGLE DROPLET ANALYSIS TO DESIGN NEBULIZER FORMULATIONS FOR TARGETED DOSING

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Summary

Hygroscopic growth of nebulized pharmaceutics is believed to be minimal as the range of relative humidity experienced by a nebulized aerosol is thought to be saturated from generation to inhalation. However, recent studies have challenged this core belief. Shown here is that nebulized pharmaceutics experience a range of relative humidities, and the potential to improve the drug efficacy of existing pharmaceutics by controlling their hygroscopic properties through the tailoring the starting formulations for targeted deposition within the lung.

Three different single droplet analysis techniques were used to analyze existing nebulizer formulations. These techniques were used to measure the necessary water activity/mass fraction of solute and water activity/density relationships to accurately model rapid droplet mass flux, and to experimentally verify the aerosol dynamic model.

The improved hygroscopic growth data were then used to predict the aerodynamic diameter of a population of polydisperse droplets from nebulization to inhalation. The treatment of the aerosol prior to inhalation (ie. changes in the relative humidity, etc.), were modelled. The size of the aerosol was input into a whole lung model based on the International Commission on Radiological Protection lung model. When integrated with the starting number density of a nebulized aerosol, the overall dose was estimated. The makeup of the starting formulation and the treatment of the aerosol prior to inhalation, were found to have a profound effect on both the overall amount and site of the dose, demonstrating the need to investigate the influence of hygroscopic response on lung deposition more completely.

21. NOVEL SIMVASTATIN PULMONARY INHALATION FORMULATION AND CHARACTERISATION

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Summary

Background: Simvastatin (SV) is an inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, used for lowering cholesterol levels in myocardial infarction prevention. Recently, there has been increasing evidence that SV possess anti-inflammatory properties and that these could be useful in decreasing the inflammation processes in chronic obstructive pulmonary disease (COPD). However, SV is chemically unstable in the presence of water/moisture. Hence, the purpose of this study was to develop a stable pressurized metered dose inhaler (pMDI) solution formulation of SV and to investigate its physio-chemical properties and aerosol performance.

Methods: Simvastatin solubility was performed visually using different concentrations of ethanol and HFA134a propellant to determine the most suitable co-solvent concentration for the formulation of a solution based SV pMDI. The short-term stability of the formulation was also evaluated at 4, 25, and 37 °C over a 2-month period and *in vitro* aerosol performance was characterised using an Andersen Cascade Impactor.

Results: SV was miscible in formulations containing 4 to 12% w/w of ethanol in HFA. The formulation containing 6% ethanol was chosen for stability and aerosol performance, since this concentration ensured SV solubility in HFA and did not lower the propellant vapour pressure to such a great extent that will affect aerosol performance. This formulation was found to be stable at all three temperatures up to two months to-date, and produced a fine particle fraction of $31 \pm 2.79\%$.

Conclusion: This study presents the formulation of a stable solution based pMDI formulation of inhaled simvastatin, which has the potential to open up new exciting anti-inflammatory therapeutic opportunities for the treatment of COPD.

22. MAXIMISING MDI SUSPENSION PRODUCT PERFORMANCE VIA SONIC PROBE PROCESSING

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Summary

Most Metered Dose Inhaler (MDI) products are formulated as suspensions rather than solutions and this is primarily due to solubility constraints of the active pharmaceutical ingredient/s (API/s) in the hydrofluoroalkane (HFA) based formulations.(1) In order to achieve the desired respirable performance of the product, the input API/s need to be reduced in particle size. This is typically performed by air jet milling, commonly referred to as micronisation. However, micronisation, in addition to the creation of particles of the target size; typically $< 5\,\mu$m in diameter, also creates many sub-micron particles as well as amorphous crystal regions. The latter, upon storage, can give rise to agglomerated particles which, if not effectively broken up during MDI manufacture, may adversely affect product performance. The agglomerated particle clusters behave aerodynamically as larger particles and can deposit in the throat instead of being inhaled. Hence formulations in which agglomerates are not properly broken up will exhibit sub-optimal performance which may be manifest in terms of both lowered respirability and more variable dosing behaviour.

This paper compares the use of conventional high shear mixing processing employing the rotor/stator principle, with a new process using powerful ultrasonic probes to effect de-agglomeration during MDI formulation manufacture. Malvern laser diffraction and Andersen Cascade impactor data are presented to show that ultrasonic probe processing can give rise to MDI product with a greater degree of dispersion and higher respirability than product made using conventional high shear mixing.(2)

Finally, data demonstrating successful employment of the sonic probe approach at the pilot manufacturing scale are shown, where a bulk concentrate was processed and monitored over time until full dispersion was complete.

23. MODELLING OF THE MICROFLUIDIZATION PROCESS FOR TOP INHALATION APIs

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Summary

Background: Microfluidization is one emerging size reduction technique in the field of inhalation; previous works [1] have suggested modelling equations for the involved comminution profiles, but evaluation of such mathematical relationships across different compounds is still missing.

Methods: Size-reduction of three compounds, namely fluticasone propionate (FP), salmeterol xinafoate (SX) and mometasone furoate anhydrous (MF), was performed by microfluidization of suspensions using the same model processor and operating conditions. In all cases, the final particle size after processing was within a typical inhalation range ($1.5\,\mu\text{m} < \text{Dv50} < 2.5\,\mu$m). After generating the data, different candidate models were identified through Partial Least Squares (PLS) regressions and, afterwards, fine-tuned (by reducing the number of fitting parameters) in order to minimize over-fitting phenomena and facilitate a potential mechanistic interpretation of the found relationships.

Results: The obtained results show that the size-reduction profiles of the different compounds, although apparently similar, cannot be entirely captured by previous models [1], requiring more flexible mathematical relationships; additionally, it was also found that the penalty (decrease of R^2 value) associated to the reduction of the number of fitting parameters depends heavily on the pre-set equation structure, a key indicator for the selection of the best performing model.

Conclusions: The intrinsic behaviour of microfluidization processes, across different top inhalation compounds, can be accurately captured, provided that an appropriated model structure is adopted; the suggested equation enables a mechanistic interpretation, where one of the fitting parameters is hypothesized to be related with the physical intrinsic properties of the compounds.

24. HOMOGENEITY OF AN ORDERED MIXTURE IS LINKED TO THE FINE PARTICLE FRACTION OF THE API

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Summary

Carrier based formulations (also called ordered mixtures) were produced with lactose carrier and four different micronized APIs: budesonide, beclomethasone dipropionate, carbamazepine polymorph 1 and salicylic acid, using two different micro-mixing methods; hand-shaking and tumbling blending. The formulations were assessed for homogeneity and for fine particle fraction (FPF) using a simple passive prototype device, the ''screenhaler'', in combination with the Next Generation Impactor, NGI. Pure APIs were investigated for primary particle size and also for fine particle fraction using a set up with the Turbuhaler® mouthpiece and the NGI.

FPF values obtained were in the range 7–24% for the ordered mixtures and 20–46% for pure APIs. Homogeneity results, expressed as RSD of API content, ranged from 0.5 to 16%. Unexpectedly, a clear correlation was observed between the fine particle fraction of the pure micronized API and formulation homogeneity, valid for both mixing methods. The correlation can be explained by the influence of shear forces, being a dominating mechanism in the mixing processes as well as in the fine particle test with the Turbuhaler

mouthpiece. Surprisingly, no correlation was found between the FPF of pure API and the FPF of the corresponding formulation assessed in the ''screenhaler'' device. This lack of correlation is believed to be due to the fact that different dispersion mechanisms are acting in the two tests, with high shear forces present in the former but not in the latter.

25. INVESTIGATIONS OF TIOTROPIUM pMDI SUSPENSION FORMULATIONS

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Summary

The anticholinergic, tiotropium (Tio) is a long-acting muscarinic agent (LAMA) that has gained acceptance as the first line of therapy for many patients with chronic obstructive pulmonary disease (COPD).

In this study, we evaluated the key aerosol parameters of some pressurised metered dose inhaler (pMDI) suspension formulations of Tio. The pMDI formulations contained a particulate excipient intended to aid manufacturing processes and to stabilise the Tio suspensions. The objective was to investigate the effects of excipient particle size, Tio:excipient blend ratios, and excipient physicochemical properties on the performance of suspension systems formulated in HFA 134a and HFA 227 propellants.

Formulations were prepared using commercially available inhalation grades of lactose (with different particle size ranges), (Lac, Respitose SV003 and SV010) combined in different ratios (i.e. 1:5, 1:10 and 1:25 w/w, Tio:excipient) and with two propellants (HFA 134a and 227). Initial aerosol characterisation tests indicated that the 1:5 (Tio:Lac) ratio was the most effective compared to higher excipient ratios and that the larger particulate Lac material (SV010) in HFA 227 improved performance further. Additional refinement of dose content uniformity and aerosol performance was achieved by substituting the excipient L-Leucine (Leu) in place of Lac. Leu (90–106 μm sieved fraction) in HFA 134a formulations produced consistent emitted dose data through canister life. The improved emitted dose performance may be a consequence of more closely matching the density of the excipient and the propellant.

In vitro aerosol properties of some novel suspension formulations showed similar characteristics to those of the Spiriva® HandiHaler.

26. ENHANCED CONTROL OF PARTICLE SIZE WITH MICROFLUIDIZATION AND MEMBRANE MICROFILTRATION

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Background: Particle size (PS) and particle size distribution (PSD) are two of the most important attributes when designing an inhalation drug product. A fine control of both these parameters is not easily achieved by current available technologies. The new method herein presented consists in combining a microfluidization step with a cross-flow microfiltration step. The combination of these technologies allows the production of particles with stricter limits in terms of size and distribution and therefore enables a more efficient delivery to the lung.

Methods: A microfluidizer and two hydrophilic flat sheet track-etched polycarbonate membranes (30 and 20 μm pore sizes) were used. The permeability critical flux (Jv_{crit}) and critical transmembrane pressure (TMP_{crit}) were determined. Filtration tests were conducted below the Jv_{crit}, using, as model system, a 5% (w/w) aqueous suspension of fluticasone propionate. The effects of the addition of surfactant and ultrasound were also assessed. PS and PSD of the particles in the feed and permeate were monitored by focused beam reflectance measurement (FBRM). Laser diffraction was also used for comparison purposes.

Results: The proof of concept work shows that the selected membranes are capable of efficiently classifying the feed suspension according to membrane pore size, narrowing the PSD of permeates.

Conclusions: The combination of these two technologies - microfluidization and cross-flow microfiltration - provides a greater control of PS and PSD and, therefore, it is expected to result in particles with enhanced performance for inhalation delivery.

27. *IN VITRO* PERFORMANCE CHARACTERISTICS OF THE A2A SPACER

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Background: Valved holding chamber (VHC) spacers are recommended for users unable to coordinate actuation of the pMDI with inhalation of aerosolized drug and/or to avoid potential drug-related events (e.g. high-dose inhaled corticosteroid-induced oral candidiasis). VHC use is commonplace among young children, and national/international recommendations exist for their use. Drug manufacturers routinely validate VHCs against their aerosol products to provide guidance and recommendations.

Methods: A similar *in vitro* evaluation of the new Clement Clarke A2A Spacer® VHC (A2A) has been conducted at an independent laboratory. A2A is differentiated from other VHCs by inclusion of an anti-microbial additive throughout the device- and interchangeable mask-polymers that also confers considerable anti-static properties. A2A has been investigated inter- and intra-sample, through lifetime, and compared with AeroChamber® VHC and pMDI without spacer; determining the aerosol characteristics of Ventolin® HFA. Particle size, GSD, total dose delivered, and respirable, coarse, fine and ultra-fine particle fraction data were determined using an Andersen Cascade Impactor operated to FDA methodology.

Results: There were no significant differences between A2A samples for any aerosol characteristic (F-statistic < 4.74, ns). A2A passed all functional and visual lifetime tests, with no significant post-test differences in aerosol characteristics ($t < 2.78$, ns). Both VHCs significantly affected total delivered dose and coarse particle fraction - an expected outcome, with the VHCs trapping the larger non-respirable particles.

Conclusion: The data indicate that A2A will be a useful additional VHC choice with bacterio- and fungi-static properties.

28. EMPIRICAL EQUATIONS FOR PREDICTING THE VAPOUR PRESSURE OF HFA 134A OR HFA 227EA SYSTEMS CONTAINING ETHANOL

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Summary

The vapour pressure of a Metered Dose Inhaler's (MDI's) formulation influences the atomisation process and the resultant size of the emitted droplets within the inhaler's dose[1,2]. This study presents the vapour pressure of pure HFA 134a and HFA 227ea formulations as well as formulations containing 100 μg of Beclometasone Dipropionate (BDP) per 50 μl and 5–40%w/w ethanol at 3°C, 20°C and 30°C. Vapour Pressure measurements were performed using a MMD-30E Electronic Diaphragm Gauge readable to 0.05bar.

Equations describing the vapour pressure of MDI formulations are not readily available. Therefore the Antoine equation[3] (Eq. 1) has been used to correlate experimental vapour pressures between temperatures of 3–30°C.

$$P = EXP(A - B/(T + C)) \quad (1)$$

Where, P=Vapour Pressure (Bar), T=Temperature (°C), and A, B and C are Antoine coefficients that vary from substance to substance.

Utilising regression software, coefficients A, B and C have been determined and empirical equations 2 and 3 were derived for HFA 134a and HFA 227ea systems respectively. Coefficients B and C were determined to be dependent upon ethanol content, E, (% w/w) for each propellant system.

$$P = EXP(3.28 - (86.37 + 0.91^{*}E)/(T + (37.91 + 0.35^{*}E))) \quad (2)$$

$$P = EXP(2.83 - (79.85 + 1.24^{*}E)/(T + (36.32 + 0.35^{*}E))) \quad (3)$$

Where, $3°C \leq T \leq 30°$

Equations 2 and 3 enable the predicted vapour pressures of pure and binary mixtures from knowledge of MDI ethanol content and temperature. There was an excellent correlation ($R^2 > 0.99$) between the experimental and calculated vapour pressure values over the range of formulations (0–40%w/w ethanol) and temperatures (3°C–30°C) evaluated.

29. D-OPTIMAL APPLICATION AS EFFICIENT TOOL DURING FORMULATION FEASIBILITY STUDIES OF NOVEL MDIs DRUG PRODUCTS

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Summary

The chemical stability of pressurized Metered Dose Inhaler (pMDI) solution formulations can be affected by many variables, such as packaging components, formulation composition, and manufacturing process. Screening all the variables that could potentially have an impact on the chemical stability of the active ingredients can imply a heavy workload, high costs, and a very time consuming step in formulation feasibility. In this paper, a traditional approach for the screening of variables is compared against a multivariate approach. These 4 variables, valve type, canister type, headspace air presence, and storage conditions, were investigated for their influence on active ingredient chemical stability. In particular, 4 different types of canister, 3 different types of valve, the presence or removal of the air in the canister headspace, and 2 different types of storage conditions were considered. All samples were manufactured using two-stage pressure filling equipment; using a validated HPLC/UV method, the active ingredient % residue assay versus the time zero value was evaluated as a main response. One Variable At A Time (OVAT) and Design of Experiment (DoE) approaches were compared. Among the possible DoE, D-Optimal design was selected. To evaluate the chemical stability using the OVAT approach, all 48 ($4 \times 3 \times 2 \times 2$) possible variable configurations were tested in triplicate (144 tested samples), whereas the application of only the D-Optimal Design would have required merely 48 samples.

It was demonstrated that the application of the D-Optimal Design allows one to obtain easily interpretable information reducing the workload by about 70%.

30. PRODUCTION AND ANALYSIS OF A SPRAY DRIED POWDER FORMULATIONS OF A MAGNETIC RESONANCE IMAGING (MRI) CONTRAST AGENT

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This paper describes the production of a spray dried formulation of Gadovist®, a magnetic resonance imaging (MRI) contrast agent.

Gadovist® is typically administered prior to the performance of an MRI to enhance the visual image by increasing the relaxation signal detected by the scanner. However, it is only available as a 1 ml solution for *iv* administration. For our clients study, a dry powder formulation was desired to enhance the image of the lung. To achieve lung deposition, a particle size of less than 3 μm would be required. It was agreed that spray drying would be used to produce a microparticle of Gadovist® as this offered the opportunity to accurately control the micro-particle size.

The Gadovist® solution was diluted with ethanol and water and spray dried using a Buchi B-191 fitted with a Schlick 2-fluid nozzle with 0.6 mm liquid insert. The liquid feed rate of 3 ml/min, atomisation at 3bar pressure, inlet

temperature 60°C, outlet temperature maintained at 46°C and aspirator set at 100%

In vitro characterisation of the micro-particles by laser particle sizing using a SympaTec HELOS gave a volume mean diameter (VMD) of 2.9 μm (d_{50}=2.5 μm). Analysis of the material using a simple device and a multi-stage liquid impinger demonstrated a mean fine particle dose of 33 mg (30–37 mg) from a mean delivered dose of 69 mg (64–76 mg).

The material was subsequently used in an *in vivo* MRI study which benefited from the enhanced visual image provided by the contrast agent being deployed to the deep lung region.

31. INTERACTION OF INHALED THERAPEUTICS WITH DRUG TRANSPORTERS IN EPITHELIAL AIRWAY CELL CULTURES

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Summary

The interaction of inhaled drug molecules with transporter proteins in the airway epithelium is poorly understood, and its clinical significance is largely unknown. This series of experiments aimed to investigate if inhaled drug compounds interact with transporter-mediated trafficking by similar mechanisms in the bronchial and alveolar epithelium. Furthermore the impact of continuous exposure to low concentrations of inhaled therapeutics on drug accumulation in *in vitro* airway epithelial models was assessed. Both salbutamol and fluticasone significantly increased the accumulation of the P-gp substrate rhodamine-123 (rh-123) in Calu-3 and A549 cells after 17 days in culture. Whilst the increased rh-123 accumulation is likely to be mediated by inhibition of the efflux transporter P-glycoprotein (P-gp) in A549 cells, in Calu-3 cells the data indicated that rh-123 accumulation was driven by an energy-independent and verapamil-insensitive pathway. A549 cells exposed to 100 μM salbutamol and fluticasone for 14 days showed a significant increase ($p < 0.01$) in rh-123 accumulation by 196 ± 3.2 and 158 ± 2.8% respectively. This work suggests that inhaled drugs do impact the transporter-mediated trafficking of compounds in both the alveolar and bronchial epithelium, but are likely to do so through different mechanisms. Furthermore, these studies provide evidence that long term exposure to inhaled therapeutics may impact airway pharmacokinetics, however further studies need to be conducted to establish the specific mechanisms involved and potential transporters implicated in these findings.

32. DEVELOPMENT OF A SPRAY DRIED TACROLIMUS FORMULATION SUITABLE FOR DELIVERY VIA A DRY POWDER INHALER

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Tacrolimus is used as an immunosuppressant following transplant surgery. A dry powder inhaled form could be of advantage to lung transplant patients by improved targeting of the therapy and the reduction of systemic side effects. The aim of the research was to produce spray dried tacrolimus formulations, investigating the effects of the addition of a bulking agent and of blowing agents. Batches were manufactured from 50:50 vol% aqueous ethanol solution using Vectura's bespoke small scale spray drier. The performance of the formulations was then assessed by cascade impactor testing using Vectura's unit dose device or multi-unit dose Gyrohaler® device. Inclusion of trehalose or a blowing agent in the formulation greatly improved blister clearance and doubled the FPF (≤ 3.3 μm) compared to a pure tacrolimus powder. Comparable results were achieved using both devices. The two lead formulations – tacrolimus (20% blowing agent) and tacrolimus /trehalose 1:1 (20% blowing agent) - were filled into unit dose blisters and sealed in foil pouches for six months with little change in the performance at 25°C/60%RH with only a small decrease in FPF and FPM at 40°C/75%RH.

Spray dried powder formulations of tacrolimus have been successfully developed at a small scale using Vectura's spray drying and formulation technology. The resulting formulations were successfully tested with both unit dose and multi-unit dose devices.

33. AN INHALABLE RIFAPENTINE DRY POWDER TARGETING LATENT TUBERCULOSIS INFECTION

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Background: One third of the world population retains latent tuberculosis infection (LTBI) with a lifelong risk of developing active disease. It was recently demonstrated that two months of daily oral rifapentine in a mouse model of LTBI was as effective as the existing 9-month isoniazid regimen. Difficulties with oral dosing of rifapentine due to high plasma protein binding (97%) may be overcome by inhaled administration.

Methods: *In vitro* characterisation of an inhalable crystalline form of rifapentine included aerosol performance, particle sizing, x-ray diffractometry and resazuarin assay. Murine pharmacokinetics compared intratracheal to intraperitoneal delivery of rifapentine.

Results: The powder consisted of elongated crystalline particles with a mass median aerodynamic diameter of 1.68 ± 0.03 μm, geometric standard deviation of 1.72 (StDev < 0.01) and a fine particle fraction of 83.2 ± 1.2%. The minimum inhibitory concentration (MIC) of the rifapentine powder was 1 ng/mL consistent with unprocessed rifapentine. Bronchoalveolar lavage (BAL) concentrations were maximal soon after administration at 0.5 hours (25 ± 6 μg/mL), declining down to 1.9 ± 1.1 μg/mL by 24 hours. Lung concentrations peaked at 321 ± 99 μg/g at 2 hours, plateauing from 12 hours onwards at 60 ± 32 μg/g. In

contrast, intraperitoneal delivery only imparted 1–4 μg/g of rifapentine to lung tissue at various time-points throughout the 24 hour time period, whilst no rifapentine was detected within the BAL.

Conclusions: Substantial rifapentine concentrations within the pulmonary site of infection can be achieved using inhaled delivery and may realise significantly shortened LTBI treatment times.

34. AEROSOLIZED TARGETED NANOERYTHROSOMES CONTAINING FASUDIL, A RHO-KINASE INHIBITOR, FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

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Pulmonary arterial hypertension (PAH) is a life threatening disorder of cardio-pulmonary system that affects individuals of all ages. Recently, it has been established that Rho-kinase mediated vasoconstriction and vascular remodeling play important roles in the pathogenesis of PAH and fasudil, a Rho-kinase inhibitor, reduces mean pulmonary arterial pressure (MPAP) in recent studies. The purpose of the present study was to evaluate the potential of CAR conjugated nanoerythrosomes (NERs), erythrocyte based biomimetic carriers, containing fasudil for targeting pulmonary vasculature that can selectively and effectively reduce MPAP. We prepared NERs by using hypotonic lysis and extrusion method. NERs were optimized for size, shape, drug loading, stability, *in vitro* release, cellular uptake followed by *in vivo* efficacy and safety. Results demonstrate that NERs were spherical in shape with an average size of $\sim$150 nm. Approximately 50% drug loading was achieved and formulation was suitable for inhalation. There was minimal change in size and entrapment when NERs were stored at 4°C for three weeks. We also showed that CAR peptide can be conjugated on the surface of NERs and they showed more propensity to bind to TGF-beta activated cells. *In vivo* efficacy experiments show that peptide conjugated formulations showed long term reduction in MPAP ($\sim$70%) as compared to plain NERs. Further, NERs were completely sage for pulmonary administration as shown by reduced levels of LDH, ALP and less edema formation in animal lungs. Overall, this study investigates and suggests the potential of a targeted and inhalable controlled release formulation of fasudil for the treatment of PAH.

35. FUNCTIONALITY OF A FACEMASK DATALOGGER WITH VALVED HOLDING CHAMBER: PRELIMINARY DATA OF APPLICATION FORCE FROM PARENTS WITH ASTHMATIC CHILDREN

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Background: For good lung deposition, when using a pressurized metered dose inhaler (pMDI) with valved holding chamber (VHC) and facemask, it is essential that the facemask provides a good seal, and comfortable fit. Actual parameters for *in vitro* bench testing of newly developed facemasks, to predict clinical use, are not well known. For this reason, a custom instrumented OptiChamber Diamond VHC with medium LiteTouch facemask, known as the Facemask Datalogger, was developed to measure application force and air flow through the VHC and facemask. The aim was to test usability of the Facemask Datalogger and to collect *in vivo* data using the Facemask Datalogger. Outcomes were application force (measured as weight), and time needed to empty the VHC (T_{VHC}).

Methods: Thirty asthmatic children aged 1–5 years, already using a pMDI/VHC with facemask. Using the Facemask Datalogger, one parent applied the facemask on the child simulating normal inhalation, and force and flow were recorded. This was repeated 3 times.

Results: Mean application force: 411 g (SD $\pm$ 161). Intersubject variability of mean force: 39% (CV) and mean intrasubject variability of mean force 23% (CV). Mean (T_{VHC}): 6.9 s (SD $\pm$ 5.5), and T_{VHC} was significantly negatively correlated with age ($r = -0.6$; $p < 0.001$).

Conclusion: The Facemask Datalogger is a useful tool to measure *in vivo* application force on a facemask and air flow through a VHC. Mean force measured was lower than that referenced in previous *in vitro* studies. These results will assist development and testing of new facemasks *in vitro*.

36. EFFECT OF A NEW TRAINING DEVICE ON pMDI TECHNIQUE AND AEROSOL PERFORMANCE

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Background: Poor MDI inhaler technique will undermine patient treatment and disease control. A small, simple, audible-tone device (In-Check Flo-Tone®), which attaches by push-fit to the pMDI mouthpiece, has been developed to teach patients when to actuate and how to achieve an appropriate inspiratory flow rate.

Methods: We report the results of two studies: an *in vitro* study (using standard Cascade Impactor techniques) to assess the effect of the device on the aerosol performance of four commercial pMDIs, and a four question ability-statement survey to determine any change in pMDI technique before and after training.

Results: The device did not affect the proportion of respirable particles (mean $\pm$ SD expressed as % valve label with/without Flo-Tone, respectively, for Ventolin® (salbutamol) 38.4 $\pm$ 2.8 / 40.1 $\pm$ 1.6; ProAir® (salbutamol) 27.2 $\pm$ 2.3/ 27.1 $\pm$ 0.3; Clenil® (beclometasone) 15.6 $\pm$ 1.8 / 14.7 $\pm$ 2.7; and Atrovent® (ipratropium) 18.0 $\pm$ 0.2 / 19.4 $\pm$ 2.0) but did capture a significant proportion of the non-respirable coarse fraction (*$P < 0.05$). From the survey sample (n=27), significant improvement ($P < 0.05$) in overall assessment of patient technique and in ability to generate and to maintain an adequate inspiratory flow was apparent following training with the Flo-Tone.

Conclusion: The results suggests that the device can be used in training to improve pMDI technique and with drug-pMDIs to act as a small spacer-like attachment to ensure good technique is maintained.

37. INVESTIGATING THE POTENTIAL OF AN AIRFLOW-INDICATING MINIATURE SPACER TO MANAGE HUMAN FACTOR BARRIERS TO EFFECTIVE METERED DOSE INHALER USE

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Abstract

Pressurized metered dose inhalers (pMDIs) qualify as 'old technologies' with the device rapidly approaching its 60th anniversary. Despite their popularity, pMDIs are associated with several difficulties, including extensive throat deposition and the requirement to coordinate actuation and inhalation. The Flo-Tone is a miniaturized spacer which aims to promote coordination by providing an aural stimulus to patients of inhalation. The aim of this work was to investigate aerosolization of two suspension pMDIs when combined with the Flo-Tone. Aerosolization was studied using the next generation impactor at 30 or 60 $Lmin^{-1}$ for salbutamol sulphate (SS – Ventolin Evohaler) and fluticasone propionate (FP – Flixotide Evohaler) products. Poor co-ordination was simulated for FP by delaying initiation of airflow through the NGI for 0.5–1.0 s after actuation. Throat deposition was reduced at both flow rates (e.g. SS $23.0 \pm 4.1\%$ to $11.9 \pm 4.3\%$ at 30 $Lmin^{-1}$) for both formulations (e.g. FP $78.9 \pm 3.9\%$ (poor coordination) to $15.73 \pm 2.09\%$). The fine particle fractions (FPF %ED) were similar for FP with ($34.4 \pm 2.5\%$) and without the spacer ($37.9 \pm 3.1\%$). It was found that the FPF %ED for SS increased when the airflow rate was increased from 30 to 60 $Lmin^{-1}$ ($46.1 \pm 2.4\%$ vs. $60.8 \pm 2.3\%$), however using the Flo-Tone overcame this effect. An airflow-indicating spacer may offer benefits by improving coordination, but was also effective at minimizing ballistic *in vitro* deposition, albeit with potential dependence on formulation identity.

38. TOWARDS STANDARDIZING METHODOLOGY FOR QUANTIFYING THE FINE PARTICLE MASS (DOSE) OF ACTIVE PHARMACEUTICAL INGREDIENT (API) FROM NASAL PRODUCTS (NPs)

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Summary

Pharmacopeial methods for the assessment of inhaled nasal products (NPs), including nasal pressurized metered-dose inhalers and aqueous spray pumps, lack clearly defined methodology for determining the mass of fine particles that may penetrate beyond the nasopharynx and deposit in the airways of the lungs with undesirable consequences. A multidisciplinary team of the European Pharmaceutical Aerosol Group (EPAG) has undertaken an experimental assessment of methods to determine this parameter. This evaluation involved development and testing of a new induction port intended to simulate the discharge of a NP into the nasal cavity, using a cascade impactor (CI) to provide fine particle dose $< 10\,\mu m$ aerodynamic diameter (FPD). This approach could form the basis for new Ph. Eur. methodology that would support the requirements of an EMA guidance on pharmaceutical quality of NPs.

39. ELECTROSTATIC STABILIZATION OF HFA pMDI SUSPENSIONS: A CASE STUDY

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Summary

Pressurized Metered Dose Inhalers (pMDIs) are established pulmonary drug delivery systems available to patients and physicians since the mid-1950s. pMDIs are formulated either in the form of a suspension or solution depending on the physico-chemical properties of the drug substance. In the case of suspension formulations fast agglomeration/flocculation of the suspended particles can present serious challenges to the formulation scientists, potentially leading to unacceptable variable pulmonary drug delivery. Additionally, crystal growth of suspended particles, due to partial solubility of the drug in the propellant system, can cause a shift in the primary particle size distribution and resulting dose delivery over time. Steric stabilization has been the most commonly used approach to achieve satisfactory physical stability of pMDI suspensions. Electrostatic stabilization is a well-known method of particulate stabilization in aqueous systems but its use in pMDI suspensions has not been utilized due to lack of experimental evidence. This paper presents a case study on successful application of electrostatic stabilization of hydrofluoro-alkane (HFA)-based suspension formulations of a Novartis investigational drug. Formulations containing micronized drug, aqueous solutions of specific electrolytes (NaCl and NaOH), ethanol and HFA134a or HFA227ea were prepared. Effective reduction of particulate flocculation and sedimentation/creaming compared to control formulations containing no electrolytes was proven over a short term stability program in terms of ex-valve dose delivery performance (i.e. mean dose and dose uniformity) and time lapse photography. Satisfactory aerosolization performance was also demonstrated over stability by Next Generation Impactor testing. In addition, chemical stability data of the selected formulations are presented.

40. DYNAMIC SUSPENSION DRYING FOR OSTWALD RIPENING PHENOMENA CONTROL

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Summary

For the engineering of Mometasone Furoate Monohydrate (MFM) to a final Particle Size Distribution (PSD) within the

inhalation range, microfluidization of the API suspension was performed, followed by isolation by spray drying. The microfluidization stage ended with a D50 $\sim$2.1 μm; however, during spray drying, increasing values of particle size were observed over time on the final dried material fractions.

To study whether the observed PSD instability on the dried powder was caused by Ostwald Ripening (OR) phenomenon of the API in suspension, two suspensions of MFM were microfluidized to a different final PS and stored at different temperatures. The observed PSD growth followed a profile that can be ascribed to OR, being dependent on both temperature and initial PSD.

In order to overcome PSD growth in suspension, an innovative engineering approach was put in place: Dynamic Suspension Drying (DSD). According to DSD, the suspension, after being processed by microfluidization at elevated pressure (and the PSD has plateau at the target values), is isolated in the form of a dried powder while continuously recycling the suspension to the microfluidization unit at an optimized mild pressure. These mild conditions prevent any increase or any reduction in the PSD, since only particle growth by OR is being prevented.

DSD was successful in preventing OR without the need of stabilizing agents, offering a substantial advantage over other approaches, because it is a much simpler and effective process that will not impact the final product properties (e.g., stability, bioavailability, performance, composition) or manufacturability.

41. ALBUMIN NANOPARTICLES FOR DRUG DELIVERY TO THE LUNGS - *IN VITRO* INVESTIGATION OF BIODEGRADATION AS A MECHANISM OF CLEARANCE

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Summary

Albumin nanoparticles are already in use in the clinic for injected delivery of the anti-cancer drug paclitaxel (Abraxane®), but as yet little research has been undertaken into their use for pulmonary drug delivery. Through SPECT/CT imaging studies, we have demonstrated their potential as a controlled release system in the lung due to their modified clearance profile compared to non-particulate albumin. Following on, the aim of this study was to investigate whether BSA nanoparticles were biodegraded by proteases at concentrations found in lung epithelial lining fluid. This is crucial for effective drug release, and also important for the clearance of nanoparticles from the lung to avoid accumulation on repeat dosing. We have investigated protease digestion of bovine serum albumin nanoparticles at a physiological protease concentration using a model enzyme (trypsin) in *in vitro* simulants of lung lining fluid using UV/Vis absorption, dynamic light scattering (DLS) and transmission electron microscopy (TEM). In a simple trypsin system, after 4 h at least 60% of BSA nanoparticles were broken down, with over 77% being digested after 48 h. In a more complex protein-supplemented medium, over 79% of particles were fully digested at 48 h. DLS and TEM were used to investigate particle sizes and distribution over 48 h. This particle digestion over a 48 h period suggests that albumin nanoparticles have potential for use as a controlled release system with a biodegradation rate that alleviates concerns about accumulation and related toxicity of nanoparticles in the lung.

42. THE EFFECTS OF SALBUTAMOL SULPHATE AND MANNITOL ON CILIARY BEAT FREQUENCY: A COMBINED THERAPY FOR MUCUS HYPER-SECRETION IN PULMONARY DISEASES

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Background: Two of the major characteristics of chronic obstructive pulmonary disease (COPD) are inflammation of the airways and hyper-secretion of mucus. Current therapies to treat these symptoms include bronchodilators and anti-mucolytic therapy. This study focuses on the co-engineering of salbutamol sulphate (SS), a common bronchodilator and mannitol, an anti mucolytic, as a potential combination therapy for COPD. This combination was chosen to have an augmented effect on the airways: the SS will act on the β_2 receptor for relaxation of smooth muscle, while mannitol will decrease mucus viscosity, consequently enhancing its clearance from the lung. A series of co-spray dried samples, containing therapeutically relevant doses of salbutamol and mannitol were prepared and tested in terms of physico-chemical characteristics. Additionally the formulation was evaluated for its effect on epithelial cell viability, transport and cilia beat frequency.

Methods: Mannitol (MA) with different concentrations of salbutamol sulphate was co-spray dried to obtain dry powders within a respirable range. The ratios (% w/w) were: 100% MA, 99.95% MA: 0.05% SS, 99.9% MA: 0.1% SS and 99.8% MA: 0.2% SS. The particles size and the morphology were analysed using a Mastersizer and scanning electron microscopy (SEM). The toxicity of MA and SS was tested on Calu-3 bronchial epithelial cell lines at different concentrations, using a liquid covered culture.

Results: The dry powder formulations showed a median volume diameter of 3.16 ± 0.46 μm, suitable for inhalation therapy. Toxicity studies have shown that both MA and SS are not toxic to the Calu-3 over the concentration range studied. Furthermore, SS 10^{-6} M, MA 10^{-3} M and the combined ratios gave a significant increase in cilia beat frequency compared to the control.

Conclusion: These studies have established that co-spray dried combination formulations of mannitol and salbutamol sulphate can be successfully prepared that have limited toxicity, good aerosol performance and increase the ciliary

beat frequency (CBF) for improving the mucociliary clearance in patients, whilst simultaneously acting on the underlying smooth muscle.

43. DO DRUG TRANSPORTERS INFLUENCE THE DISPOSITION OF INHALED DRUGS?

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Drug transporter effects on pulmonary PK have been hypothesised for several years and a number of *in vitro* studies presented data consistent with this hypothesis. Transporters may alter airway residence times of drugs, modulate access of drugs to intracellular targets and submucosal lung tissue, and potentially influence drug absorption profiles into and from the systemic circulation. Recent studies in experimental animal models and human volunteers, for the first time, support the idea that drug-transporter interactions are indeed a clinical reality. Particularly, the family of ATP-binding-cassette (ABC) transporters - to which many efflux pumps belong – has been associated with increased airway retention time of inhaled bronchodilators, i.e., β-agonists and anti-muscarinics. Consequently, inhibition of these transporters by drugs such as verapamil, which is frequently used by patients suffering from co-morbidities like hypertension, has profound implications on local drug concentrations at the target receptors, but also systemic exposure and side effects. In the same context, it is important to confirm if our currently available *in vitro* models are powerful enough to predict *in vivo* findings.

44. VALIDATION OF THE ALICE-CLOUD TECHNOLOGY FOR FUNCTIONAL EFFICACY STUDIES WITH AEROSOLIZED DRUGS DELIVERED TO CELLS AT THE AIR-LIQUID INTERFACE

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Summary

Background: Aerosol-based inhalation therapy is widely used for the treatment of lung diseases, but reliable drug screening approaches in complex phenotypic settings (e.g. cell systems) at the air-liquid interface (ALI) are unavailable. Here, we introduce the ALICE-CLOUD technology, which utilizes the principles of cloud motion for delivery of bioactive aerosolized liquid drugs to pulmonary cell types cultured under physiologically realistic ALI conditions.

Methods: Drug-to-cell delivery efficiency of the ALICE-CLOUD was investigated with fluoresceine as surrogate drug. A novel candidate drug for anti-inflammatory inhalation therapy Bortezomib (Velcade®) was investigated by stimulating human alveolar epithelial cells (A549) with TNFα resulting in a 7–8-fold activation of the IL-8 promoter. Bortezomib (Velcade®) was applied to the cells and the effect on IL-8 promotor activation and proteasome activity was investigated in cell lysates using a luciferase reporter assays. Cytotoxicity was monitored with the WST-1 and LDH assays.

Results: For 200 μL of nebulized liquid, 33.6 μL was delivered within 3.5 min to 6-well transwell inserts (5.6 μL per insert) corresponding to a 16.8% delivery efficiency. The reproducibility of the dose was 9.3% and the insert-insert variability was 4.3%. We found that Bortezomib (Velcade®) can be aerosolized to efficiently block proteasomal activity and mediate potent anti-inflammatory effects in A549 cells cultured at ALI conditions. Importantly, aerosolized and liquid (non-aerosolized) drug delivery showed identical drug efficacy. Of note, the response kinetics of aerosolized Bortezomib was by about a factor of 12 faster than non-aerosolized Bortezomib delivered under submerged conditions.

Conclusion: Our data validate the ALICE-CLOUD as an easy-to-handle, quantitative, and highly suitable tool for preclinical screening for inhalation drugs at realistic conditions. Moreover, we identify Bortezomib – and possibly also other representatives of this class of biopharmaceutics - as a promising candidate for inhalation therapy.

45. UNDERSTANDING THE AFFECT OF DPI DEVICE AND LACTOSE TYPE ON THE OUTPUT FROM A DEVICE

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Dry powder device are more complicated to design and develop then pMDI and nasal devices. During the development process there are three components to optimise for a device to work correctly, device, API and lactose. Each component has a range of complex interaction which impact on how the final device will perform. On the device a designer/developer will consider a range of issues such as, type of material, how the dose will be delivered, how to maintain the uniformity and will the device be a single dose or multi dose, and also need to be easy to use. API and lactose performance is subject to, particle size, particle shape, type of production, mode of blending, how they fluidise and breakup to release the API, all play a role in the optimisation of the final product. The aim of the paper was to assess, change in the output from a Easyhaler® standard reservoir DPI device with 3 types of lactose, *Respitose® SV003, Respitose® ML001 and Lactohale® 300*. The following parameters were measured, plume angle, event duration and intensity profile of lactose from the device. The results show, for plume angle and event duration there was no significant difference between *Respitose® SV003* and *Respitose® ML001*. The results for *Lactohale® 300* are significantly different. The intensity profile results provide some insight in to how the material flows from the device and the release profile for each combination. *Lactohale® 300* profile is different, to that of *Respitose® SV003* and *Respitose® ML001*, with a slow decay over the event. This may in part be due to the small size range (D50 < 5 um) and the mechanisims involved in the fluidisation and agglomerate breakup of the powder from the device.

46. EVALUATION OF PLUME GEOMETRY AND SPRAY PATTERN FROM DRY POWDER DEVICES USING FDA GUIDANCE

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Summary

General plume characterisation first became a regulator requirement in 1998[1], with the introduction of the CMC draft guidance on pMDI's and DPI device. The document outlined the basic data requirement for spray pattern and plume geometry measurement for pMDI device. The requirements are designed to monitor consistency and quality of a devices when actuated. In 2008 guidance for Nasal products on BABE (Bioavailability and Bioequivalence)[2] provided details on data required and the distances where pattern information are obtained. In 2013 *in vitro* / *in vivo* study for pMDIs[3] start to implement the same requirement as those laid down in the nasal guidance in 2008[2]. At present there are no requirement for the measurement on plume geometry and spray pattern for DPI devices, because of the complexity of imaging the powder flow from DPI devices. The poster outlines the techniques used for the evaluation and implementation of FDA guidance on DPI devices. A vacuum pump operating at 50 l/min extracts powder from the DPI device through OL test chamber. FDA guidance[1,2], provide details on plume geometry and spray pattern, image collection and evaluation. The spray patterns were collected at 2 distance 3 cm and 6 cm from the exit of the device. The results show the plume geometry varies between 15 & 17 degrees across 3 replicates with mean event duration of 82 ms. The spray pattern ovality results at 3 cm show 12.7% variation & 6 cm results show 6.1% variation. The poster clearly shows that FDA guidance can be applied to DPI devices.

47. SYNTHESIS OF CURCUMIN NANOPARTICLES FOR LUNG CANCER THERAPY

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Summary

Most drugs in cancer therapy are associated with serious side effects owing to non-specific cellular uptake of chemotherapeutic drugs by both cancerous and normal cells. Plant extracts are considered for cancer therapy, as they possess high antioxidant and anticancer activities. Curcumin (diferuloylmethane), the active ingredient from tumeric extract, has gained momentum as a potential cancer drug. It possesses high selectivity towards cancer cells while exerting negligible systemic toxicity towards healthy cells, even at higher doses. In this study, curcumin nanoparticles, Cur-NP (28 to 200 nm) were engineered as inhalable drug for lung cancer therapy. The effectiveness of Cur-NP to kill lung cancer cells was evaluated using two models lung carcinoma cell lines, A549 and Calu-3. A non-cancerous lung cell line, BEAS-2B, was used as control. *In vitro* cell study showed that engineered Cur-NPs have higher cytotoxicity effect on lung cancer cell lines A549 and Calu-3, compared to raw curcumin. The cytotoxicity effect was size-dependent, with the smallest nanoparticles exerting superior activity. Higher cytotoxic effect was further supported by higher internalization of Cur-NP into these cancer cells. Qualitative results by confocal microscopy showed that Cur-NP (28 nm) had higher uptake and internalization, with Cur-NP present in the nucleus. Interestingly, Cur-NPs were not toxic to normal healthy cells (BEAS-2B). In conclusion, Cur-NPs have been demonstrated to be suitable for lung cancer treatment by pulmonary administration.

48. COMBINATION THERAPY OF CURCUMIN AND SILVER NANOPARTICLES WITH ENHANCED ANTI-BIOFILM ACTIVITY FOR TREATMENT OF ENDOTRACHEAL TUBE-ASSOCIATED INFECTIONS

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Summary

Biofilm tolerance has become a serious clinical concern in the treatment of nosocomial pneumonia owing to the resistance to various antibiotics. There is therefore an urgent need to develop alternative antimicrobial agents or combination drug therapies that are effective via different mechanisms. Silver nanoparticles (AgNP) have been developed as anti-biofilm agent for the treatment of infections associated with the use of mechanical ventilations, such as endotracheal intubation. Meanwhile curcumin, a phenolic plant extract, has displayed natural anti-biofilm properties through the inhibition of bacterial quorum sensing systems. The aim of this study was to investigate the possible synergistic/additive interactions of AgNP and curcumin nanoparticles (Cur-NP) against both Gram-negative (*Pseudomonas aeruginosa*) and Gram-positive (*Staphylococcus aureus*) microorganisms. The combination therapy against *P. aeruginosa* showed an additive effect with minimum inhibitory concentration (MIC) of 29.4 μg/mL. Similarly, it was found that the MIC of Cur-NP alone against *S. aureus* was 220 μg/mL, compared to 50 μg/mL for the combination therapy. Combination of AgNP and Cur-NP (termed as Cur-SNP) at $\sim$100 μg/mL disrupted 50% of established bacterial biofilms (formed on microtiter plates). However, further increase in the concentration of Cu-SNP failed to effectively eliminate the biofilms. To achieve the same effect, at least 500 μg/mL of Cur-NP alone was needed. Scanning electron microscopy (SEM) and confocal laser scanning microscopy (CLSM) revealed that combination

therapy (Cur-SNP) was the most potent to eradicate pre-formed biofilm compared to mono-drug therapy. These agents are also non-toxic to healthy lung cells (BEAS-2B). As a co-therapy, curcumin acts to inhibit biofilm re-assembly and production of virulence factors in biofilm while AgNP inactivates cells activities through binding with sulfur-based compounds.

49. CLINICAL PHARMACOLOGY AND PHYSIOLOGY OF AGEING: IMPLICATIONS FOR DRUG THERAPY

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Summary

The size of the oldest old section of the population is rising and as a consequence the prevalence of frailty is rising. The physiological changes with age have important implications for both the pharmacokinetics and pharmacodynamics of drugs. Changes in pharmacokinetics include the reduction in renal clearance of water soluble substances including drugs such as aminoglycosides, lithium and digoxin. These examples are of drugs not only cleared renally but also with a narrow therapeutic window making the risk of toxicity much higher. The physiological reduction in liver volume reduces the hepatic clearance of lipid soluble drugs. In addition, the increase in the proportion of lipid tissue per kg body weight (increasing the apparent volume of distribution) increases the elimination half life (t1/2 z) of lipid soluble drugs independently of the prolongation due to reduced clearance. In addition to these changes caused by age related physiology, frailty is associated with further prolongation of t1/2 z. Other age related physiological changes with important implications for clinical practice include changes associated with less efficient homeostasis such as reduced baroreflex efficiency and reduced efficiency of balance maintenance. These changes may be potentiated by prescribed medication. Cognitive ageing is associated with reduced attention and decline in some types of memory as well as slower processing. These effects however are very small in magnitude compared to the effects of pathology such as Alzheimer's disease. Dementia of any aetiology will adversely affect both compliance with medication regimens as well as the technique of administration where relevant.

50. DESIGN CONSTRAINTS IMPACTING DEVELOPMENT OF INHALED ANTIBIOTICS IN PORTABLE DRY POWDER INHALERS

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Formulation of dry powders comprising engineered PulmoSphere™ particles enable delivery of high doses of antibiotics to the lungs with a portable dry powder inhaler. This leads to significant reductions in treatment time and improved convenience relative to delivery with standard jet nebulizers. Cystic fibrosis (CF) patients, including pediatric patients and patients with severe lung disease can effectively empty and disperse PulmoSphere powders from a passive capsule-based dry powder inhaler. Tobramycin inhalation powder has a safety profile comparable to the current nebulized drug product, and the inhaled dry powder is well tolerated. It is hoped that the improved convenience and shorter administration time noted with the dry powder will lead to improved adherence to therapy, and as a result improved clinical outcomes.

51. FROM POWDER TO PATIENT - OPTIMISATION OF PARTICLE SIZING TECHNIQUES

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Particle size distribution (PSD) methodology is a very complex topic but also critically important for the design and control of pharmaceutical inhalation products. There are many parameters which affect PSD data and many interactions between these parameters, so unravelling the causes of variability is notoriously difficult. There are three primary forms of particle sizing distributions (PSDs) used for characterising pMDI products: i) primary PSDs of powders by laser diffraction (LD), ii) droplet size distributions (DSD) in an ex-actuator plume by LD, and iii) aerodynamic PSDs of these droplets by cascade impactors (CI). These three forms of analytical method are discussed and some initial data is presented to show how in principle there can be correlation between the techniques for pMDI products. A mathematical model helps to improve the correlation between the geometric PSD (from LD techniques) and the aerodynamic PSD (from CI techniques) by introducing a density function based on the Stokes equation.

52. WHAT A DIFFERENCE A YEAR MAKES; 2013 REVIEW

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Summary

Events occurring during 2013 in the orally inhaled drug product (OIDP) sector are reviewed. There have been a number of acquisitions, such as Pearl Therapeutics by AstraZeneca, Microdose Therapeutx by Teva Pharmaceuticals and MAP Pharmaceuticals by Allergan. A number of smaller companies successfully raised funds to continue their product development programs and a number of collaborations were announced, such as that between Chiesi and Activaero. Significantly, more e-, i- and Apps become available, with more on the way. Most of these are aimed at ensuring the medication is taken when needed and taken correctly. These technologies allow the patient to be much more aware and responsible for their own control and compliance. Market reports predict good annual growth in product sales, especially for COPD and combination products, health organizations still predict that COPD is very under diagnosed. All major respiratory companies reported progress of their product portfolios with several license applications made and approvals received. Biomarkers for asthma and COPD are not well established, so the proposed use of plasma fibrinogen is

good news. Systemic inhaled drug delivery continues with the approval of inhaled loxapine (Alexza Pharmaceuticals). Inhaled insulin (Mannkind) may be re-submitted in Q413, whilst Dance Biopharm continues its insulin development program. Other systemic products were also progressed, especially inhaled antibiotics.

53. COMPARISON OF *IN SILICO* AND *IN VIVO* PHARMACOKINETIC DATA FOR INHALATION PRODUCTS

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Summary

Background: During the development of inhalation products, using animal models is inevitable for the evaluation of formulation. To comply with the 3R principle (reduction, refinement, and replacement of animal experiments) and to reduce costs, it is desirable to predict the efficacy of formulations based on theoretical calculations.

In the current study we evaluated the suitability of *in silico* tools to predict the *in vivo* pharmacokinetic data of inhaled drugs.

Methods: GastroPlus™ with Additional Dosage Routes Module™ was used for the simulation studies. The *in vivo* data of a metered dose of 1.0 mg budesonide after administration either by a Turbuhaler® or by a pMDI + Nebuhaler® were taken from literature and compared with the simulated data.

Results: Generally, the *in silico* data were comparable with the *in vivo*. Simulations with GastroPlus™ predicted higher bioavailability and higher plasma levels of budesonide using Turbuhaler compared to pMDI + Nebuhaler. Absolute data for bioavailability was relatively higher and plasma levels were relatively lower in GastroPlus™ than *in vivo* data. This apparent discrepancy could be due to the slow excretion rate reported in the literature. Additionally, the calculation models used for the *in silico* simulation have a great influence on the obtained bioavailability values.

Conclusion: In this study we have shown the suitability of *in silico* modeling for supporting pulmonary drug development. Such models offer a useful tool for linking the drug product properties to *in vivo* performance, enabling the implementation of Quality by Design in inhalation drug development and the reduction of animal experimentation by improved selection of candidates.

54. THE EFFECT OF CO-SPRAY DRYING WITH POLYETHYLENE GLYCOL ON THE POLYMORPHIC STATE OF MANNITOL CARRIER PARTICLES FOR DRY POWDER INHALATION

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The design of a carrier particle is important for the development of dry powder inhalation (DPI) formulations. Most DPI formulations rely on lactose as a carrier particle; however, lactose has several disadvantages with DPI formulations. In this study we focused on mannitol as an alternative carrier to lactose. Spray drying was reported as challenging to produce α-mannitol, as β-mannitol is obtained in almost all cases. The polymorphic state of a carrier particle is reported as one of the properties which affect the aerosolization performance of DPI formulations. To control the polymorphic state and to evaluate its effect for the aerosolization performance was considered to be important for the development of DPI formulations. The purpose of this study is to control the polymorphic state and to selectively produce α-mannitol by spray drying, instead of β-mannitol. The effect of polyethylene glycol (PEG) 4000 on a polymorphic state of mannitol was investigated. Powder X-ray diffraction studies showed that spray drying mannitol without PEG 4000 completely produced β-mannitol. In contrast, mannitol/PEG 4000 (PEG 4000 concentration was above 1%) co-spray dried products were found to be completely α-mannitol. It can be estimated that the molecular mobility of mannitol in the presence of PEG 4000 must have been slower than that of mannitol alone and reduced molecular mobility inhibited the transformation from α-mannitol nuclei into β-mannitol nuclei during the spray drying process. Consequently, controlling the polymorphic state and selectively producing α-mannitol by spray drying was successful by adding above 1% of PEG 4000.

55. *IN VITRO* DELIVERY EFFICIENCY OF VALVED HOLDING CHAMBERS WITH OR WITHOUT FACEMASKS

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An in vitro method has been described and refined previously for the performance evaluation of valved holding chamber (VHC)-facemask systems. The purpose of this study was to evaluate the delivery efficiency of three commercial VHC-facemask systems: AeroChamber Plus Flow-Vu VHC with ComfortSeal facemask (ACP-FV); OptiChamber Diamond VHC with LiteTouch facemask (OCD-LT); Vortex VHC with Felix Frog facemask (VTX-FR) at simulated pediatric conditions. The study comprised of standardized methods to evaluate VHC-facemask seal leakage against a soft anatomical model (SAM0) and evaluation of delivered dose under an age-specific pediatric breathing pattern which was simulated using an ASL Servo Lung. The results showed that the OCD-LT system formed an effective seal at both application forces (%leakage=47.4% at 1 lb and 46.5% at 4 lb), whereas the ACP-FV system achieved an effective seal only at high application force (%leakage=89.8% at 1 lb; 55.6% at 4 lb). The VTX-FR system did not achieve an effective seal in any test condition. Facemask seal leakage reflected delivery efficiency. The ACP-FV system had good delivery efficiency (%delivered dose=38–43%) at high application force (4 lb) but poor delivery efficiency (%delivered dose=0.7–1.8%) at low application force (1 lb).The OCD-LT system resulted in the most consistent delivered dose even at low application

forces (%delivered dose=35–42% at 1 lb, 41–47% at 4 lb). When the VHCs were tested without facemask (complete seal) they all produced a good delivery efficiency (%delivered dose; 45–55 for OCD, 41–49% for VTX, and 55–58% for ACP).

56. FUNCTIONAL EXPRESSION OF P-GLYCOPROTEIN AND MULTIDRUG RESISTANCE-RELATED PROTEIN-1 IN NCI-H441 HUMAN BRONCHIOLAR EPITHELIAL CELLS

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Background: The human bronchiolar epithelial cell line, NCI-H441 has recently been introduced as an *in vitro* model for studying drug disposition at the distal lung air-blood barrier. Here, we determined whether levels of expression and function of major ATP-binding cassette transporters, P-glycoprotein (P-gp) and multidrug resistance-related protein-1 (MRP1) in HCI-H441 cells were comparable to those in freshly isolated human distal lung epithelial cells in primary culture.

Methods: P-gp and MRP1 expression was quantified by immunoblot, whilst confocal laser scanning microscopy (CLSM) was employed to determine transporter localisation. Efflux experiments with rhodamin 123 (Rh123, P-gp substrate) and 5,6-carboxyfluorescein-diacetate (CF, MRP1 substrate) were carried out assessing transporter function *in vitro*. Furthermore, the inhibitory effects of LY-335979 (specific P-gp inhibitor) and MK-571 (specific MRP1 inhibitor) on Rh123 and CF efflux were investigated.

Results: Immunoblot provided evidence that NCI-H441 cell monolayers expressed both efflux pumps on protein level. CLSM data confirmed these observations and moreover, revealed localisation of the transporters along apical membranes and in perimembranous vesicles. Rh123 and CF were both released from NCI-H441 monolayers in a time-dependent manner. This efflux could be inhibited by the relevant pharmacological agents.

Conclusions: P-gp and MRP1 expression and activity in NCI-H441 cell monolayers were found to be consistent with data previously reported from human peripheral lung epithelial cells in primary cultures. The use of NCI-H441 cells to investigate efflux pump effects at the air-blood barrier can therefore be recommended.

57. TAKING THE EVALUATION OF ORALLY INHALED PRODUCTS IN THE LABORATORY TO THE NEXT LEVEL: INTRODUCING THE PATIENT EXPERIENCE INTO THE PICTURE

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Summary

Despite significant advances in the technology associated with the administration of all forms of inhalation therapy, patient adherence in the management of chronic conditions such as asthma and chronic obstructive pulmonary disease (COPD) is poor. The focus of laboratory testing of orally inhaled products (OIPs) has largely ignored the way in which the patient interacts with the device, paying attention instead to requirements for data obtained by methods that are simplified to achieve the necessary degree of robustness. Although such testing is clearly essential in the context of asserting product quality, regulatory agencies are beginning to recognize the need for additional information about performance that relates to the intended user experience. In this context, the drug product and delivery device, including add-ons such as spacers and valved holding chambers (VHCs) used with pressurized metered dose inhalers (pMDIs) have to be treated as a single entity. Laboratory methods simulating age-appropriate breathing patterns, poor coordination of inhaler actuation and inhalation, and the possibility that the patient interface may be a facemask rather than a mouthpiece are therefore needed. It is hoped that such approaches will eventually become incorporated into the suite of compendial methods, once validated satisfactorily. Evaluations of inhalers simulating patient use can be very useful in product design and development phases, where increasing emphasis is being placed on a risk management approach. In this way, the patient adherence problem can be better addressed with the next generation of 'patient-friendly' inhalers.

58. COMBINING INHALATION BY A BREATH-ACTUATED NEBULIZER (BAN) WITH EXHALATION THROUGH AN OSCILLATING POSITIVE PRESSURE DEVICE (OPEP) OFFERS THE POTENTIAL FOR COMBINED THERAPY

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Summary

A novel hand-held oscillating positive expiratory pressure (OPEP) therapy device (Aerobika*, Trudell Medical International (TMI), London, Canada) has been developed that can be used in conjuction with the AeroEclipse®-II breath actuated nebulizer (BAN, TMI). The Aerobika* OPEP device by itself has shown promising signs from lung imaging studies for the opening of secretion-obstructed airways. A follow-on study is reported here, evaluating how the OPEP-BAN configuration performs for the delivery of three different inhaled medications deliverable by nebulizer that might be used clinically in support of improving airway patency or reducing underlying inflammation. Combining the AeroEclipse-II® BAN with the Aerobika* OPEP therapy device reduced only slightly the overall aerosol delivery in terms of either total emitted mass (TEM) with all three formulations. The resulting aerodynamic particle size distribution (APSD) data were also slightly displaced to finer sizes by the presence of the OPEP device. These size shifts represent marginally increased retention of the coarser, less

therapeutically beneficial particles in transit through the OPEP device, most likely due to inertial effects at the valve support as otherwise the flow path contains no obstructions or bends that might increase turbulent deposition. Hence, in terms of fine particle mass (FPM), the presence of the Aerobika* device resulted in no difference for two of the three formulations (paired t-test, $p \geq 0.38$), and only a statistically marginal reduction for the third.

59. LABORATORY PERFORMANCE EVALUATION OF PROTOTYPE NASAL MASK FOR INFANTS USING THE ADAM-III INFANT FACE MODEL: PROOF-OF-CONCEPT

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Summary

The onset of symptoms related to a heterogeneous group of respiratory diseases termed Chronic Lung Disease of Infancy can take place from birth, and may require treatment with inhaled medication. The most suitable patient interface is a facemask for this group of patients. Dead-space within the facemask should ideally be minimized to avoid rebreathing as well as loss of medication by deposition within the facemask and on the face with this population, whose inhaled volume when tidal breathing can be ≤ 50 mL. Infant facial anatomy is very different from that of older children and it is therefore insufficient to merely rely on scaled down versions of adult masks A prototype nasal mask has been developed by Trudell Medical International to address this currently unmet need. A proof-of-concept laboratory study was undertaken delivering one actuation of pMDI-delivered salbutamol via an AeroChamber mini* aerosol chamber (AC), equipped with nasal mask that was applied to the nose of the ADAM-III infant face and nasopharyngeal airway model either with light or heavy force of 0.8 kg (7.8 N) and 1.6 kg (15.6 N) respectively. Tidal breathing was simulated (tidal volume=50 mL; duty cycle=25%, respiration rate=30 cycles/min). Approximately 5 μg/actuation (ca. 5% label claim dose) was able to be delivered using either applied force, representing potential medication delivery to the carina. This level is of the same order as in previously reported clinical evaluations for pMDI-delivered medications, although to infants with significant airway obstruction.

60. UNIFORMITY OF DELIVERED DOSE FROM THE FIRST TO LAST DOSE OF THE BF SPIROMAX® INHALER IN THE LABORATORY AND UNDER 'REAL-WORLD' CONDITIONS

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Summary

Budesonide/formoterol Spiromax® ([BF Spiromax], Teva Pharmaceuticals) is a dry-powder inhaler delivering budesonide and formoterol for the treatment of asthma and COPD. BF Spiromax has been developed in low strength, middle strength and high strength formulations (80 μg/4.5 μg, 160 μg/4.5 μg and 320 μg/9 μg of budesonide/formoterol per inhalation, respectively).

Dose consistency was evaluated using uniformity of delivered dose (UDD) assessments. UDD was tested using low, medium and high strength inhalers. Doses from different stages of the BF Spiromax lifespan were collected using a Dose Uniformity Sampling Apparatus. To simulate real-world conditions, inhalers were subjected to natural knocks/vibrations and temperature/humidity variations. Inhalers were assessed at the beginning, middle and end of their lifespan and UDD measured over a ≤ 90 day period until the last labelled dose. Five simulation schemes were assessed using low, medium and high strength BF Spiromax with variations in the number of inhalations twice daily.

The BF Spiromax devices delivered consistent doses throughout inhaler lifetime. Delivered doses increased in proportion with the labelled doses for each strength. Using real-world simulations, for all five schemes, UDD was also consistent throughout inhaler lifetime. Dosing regimen had no impact on UDD for each BF Spiromax formulation.

All three strengths of BF Spiromax delivered consistent doses throughout their lifetimes and over five real-world dose and schedule regimens.

61. OPTIMISATION AND CONTROL OF DRY POWDER MIXING PROCESSES USING A MIXING SENSITIVE PIGMENT

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A robust and novel method has been proposed to evaluate dry powder mixing using a mixing-sensitive colouring agent - sub-micronised iron oxide. The method measures the change in colour (hue) and hue intensity of blends over the duration of mixing and enables the analysis of two distinct mixing behaviours, namely pigment de-agglomeration (transition from red to orange) and dispersion through the bulk material (increase in the intensity of the blend's hue).

Several experimental campaigns were conducted with various inhalation grade lactoses, both free-flowing and cohesive, to observe whether blend pigmentation could serve as an indicator for mixing behaviour and phenomenon in different systems. Three mechanistically different blending technologies were predominant in the studies and blends were manufactured at a variety of operating conditions and scales.

Through colourimetric analysis of each blend over time in different mixing conditions, a series of formulation specific process curves were generated based on the population of fine lactose particles and pigment. Process curves were found to be not only be able to quantify the level of pigment dispersion and de-agglomeration, but also analyse blend uniformity, energy input and detect the generation of fine particles through milling. These results suggest that the iron oxide tracer method can be used as a simple and powerful preliminary approach to the optimisation of powder

**Trademark of Trudell Medical International and Monaghan Medical Corporation*

blending, and can potentially reduce both the cost and time traditionally associated with technology transfer or scale-up as it can show equivalent powder mixing between two systems or sets of mixing conditions.

62. DESIGN AND DEVELOPMENT OF A DISPOSABLE HIGH DOSE DRY POWDER INHALER FOR AMINOGLYCOSIDES

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Background: Currently applied nebulisation techniques for the administration of antibiotics to patients are time consuming and expensive and therefore, inappropriate for antibiotic therapies against infectious diseases like tuberculosis in developing countries. Dry powder inhalers may be an interesting alternative as they can be simple, cheap and thus, disposable which is an advantage for pulmonary antibiotic delivery. To become successful, it requires that the use of excipients is minimised and that simple production techniques are applied.

Methods: For high dose drug formulations without excipients it is required to adapt the design of the dry powder inhaler to the specific properties of the drug, which for aminoglycosides are troublesome in relation to dispersion and inhaler retention. We modified the Twincer™ for delivery of tobramycin as model compound for aminoglycosides and investigated dispersion efficiency of a spray dried product with laser diffraction technique and the inhaler retention by gravimetrical analysis.

Results: In the re-designed Twincer™, the fine particle fraction smaller than 5 μm was 75% at 2 kPa and more than 80% at 4 and 6 kPa. The inhaler retention decreased to less than 15% at all three pressure drops.

Conclusion: The Twincer™ dry powder inhaler can be optimised for spray-dried tobramycin base by re-designing the classifiers and changing the flow breakdown. This new concept is called 'Cyclops' and has a single classifier with more air inlet channels compared to the two parallel classifiers of the basic Twincer™.

63. COMPUTATIONAL MODELLING AND STOCHASTIC OPTIMISATION OF ENTRAINMENT GEOMETRIES IN DRY POWDER INHALERS

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Summary

Dry powder inhalers are one of the methods for the delivery of drug particles to the lungs. In addition to the influence of powder properties, their performance is dependent on the aerodynamics of the airpath and the user's inhalation characteristics. As a result, engineers have used computational fluid dynamics (often single-phase) to improve the aerodynamic performance of individual inhaler geometries. This paper attempts to extend this approach by using a stochastic optimisation algorithm coupled with a multiphase (air-powder) computational model to automatically evaluate multiple geometric iterations. Of the functional parts that make up the inhaler, entrainment geometries play an important role. They were therefore chosen as the focus of this optimisation study. The performance of the computational model used was in reasonable agreement with the experimental results found in the literature. Optimisation was therefore carried out for flow rate independence and dispersion of powder at the outlet – both desirable in efficient inhalers. The latter criterion appeared to be a harder optimisation problem than flow rate independence. The algorithm managed to produce plausible improved geometries (that utilised flow recirculations), although further validation studies would be needed.

64. MEASURES OF AEROSOL QUALITY: RESPIRABLE DELIVERED DOSE AND NON-RESPIRABLE DELIVERED DOSE

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The present study builds on earlier work conducted by the authors, who concluded that a high delivered dose (DD) was not necessarily indicative of a good quality aerosol; which was defined in the study as a high respirable delivered dose (RDD) and fine particle fraction (FPF).[1] The current study also aims to consider aerosol quality from a wider perspective, including not only the RDD but the non-RDD (NRDD). DD and mass median aerodynamic diameter were determined, in accordance with the methods described in CEN Standard EN 13544-1,[2] and the RDD and NRDD were calculated from these values. The results generated were in agreement with previous studies, in that a high DD from a nebulizer was not an indicator of a high RDD. Extending the study to include NRDD indicated that some nebulizers that provided a high DD and RDD, also had a high NRDD, and some nebulizers that gave a low DD, but a high RDD, had a low NRDD. Given that the NRDD is the mass of drug delivered to the patient in larger particles, which potentially impact in the oral cavity and throat, and may cause irritation to the patient, NRDD should be a measure of performance that is considered when comparing the quality of aerosol delivery from nebulizers.

1. Rehman M, et al. Clin Transl Allergy. 2013;3(Suppl 1):P10.
2. European Committee for Standardization (CEN). EN 13544-1:2007 + A1:2009. *Respiratory therapy equipment. Nebulizing systems and their components.* European Committee for Standardization; 2010.

65. DELIVERED DOSE COMPARISON BETWEEN BREATH-ACTIVATED (METERED DOSE AND NON-METERED DOSE) AND BREATH ENHANCED NEBULIZERS

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In previous studies we have looked at the variability in dose between venturi jet, breath-enhanced, and mesh

nebulizers.[1,2] In this study we extended the investigation to cover breath-activated nebulizers, comparing them to a representative breath-enhanced nebulizer. Here we report on a comparison of the delivered dose (DD) from the AeroEclipse II (AeroEclipse II; Monaghan Medical Corp.), a non-metered breath-activated nebulizer, the I-neb Adaptive Aerosol Delivery (AAD) System (Respironics Respiratory Drug Delivery (UK) Ltd), a metered breath-activated nebulizer, and the LC Sprint (PARI GmbH), a breath-enhanced nebulizer. The I-neb AAD System and the AeroEclipse II nebulizer only deliver aerosol during inhalation, but the LC Sprint nebulizer also delivers during exhalation, albeit at a reduced rate. The breath-activated nebulizers claim greater reproducibility of DD. Each nebulizer was filled with 2.5 mL salbutamol sulphate (Salamol Steri-Neb, 2 mg/mL, IVAX Pharmaceuticals) and attached to an ASL 5000 breathing simulator (IngMar Medical Ltd) set to an adult breathing pattern (tidal volume=500 mL, 10 breaths per minute, inhalation:exhalation ratio=1:2). The AeroEclipse II nebulizer and the LC Sprint nebulizer were driven by 6 L/min medical air and run until sputter plus 60 seconds. The I-neb AAD System was fitted with a 0.5 mL dosing chamber and run until the end of aerosol generation. Delivery period was recorded for all nebulizers. The results indicated that the breath-activated nebulizers allow for a more reproducible DD. The DD results from the 2 breath-activated nebulizers were significantly different, and a considerably greater DD was delivered from the AeroEclipse II nebulizer, compared to the LC Sprint nebulizer or the I-neb AAD System. If such differences in DD were replicated *in vivo*, they could be translated into clinically relevant differences in drug dose available to the patient.

1. Hatley R, et al. *Respiratory Drug Delivery 2012.* Vol. 3. 2012: pp. 663–668.
2. Hatley R, et al. *Respiratory Drug Delivery 2012.* Vol. 3. 2012: pp. 669–672.

66. DELIVERED DOSE COMPARISON BETWEEN BREATH-ACTIVATED AND BREATH-ENHANCED NEBULIZERS

S Byrne, RHM Hatley

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Different types of nebulizer are designed to have different drug delivery efficiencies, which may interact with a range of user-specific factors, such as drug formulation and breathing pattern, to affect the delivered dose. We tested 2 different types of jet nebulizer, using 2 different drugs and an adult breathing pattern, to determine the difference in aerosol delivery over time. A breath-enhanced nebulizer (LCS; LC Sprint, PARI GmbH) and a breath-activated nebulizer (AEII; AeroEclipse II, Monaghan Medical Corp.) were connected, via a filter, to a breathing simulator set to generate an adult breathing pattern (BP; tidal volume=600 mL, inhalation:exhalation ratio=1:2, 10 breaths per minute). Each nebulizer was loaded with salbutamol sulphate (2.5 mg/2.5 mL, Salamol Steri-Neb, IVAX Pharmaceuticals) and run with the BP for 20 minutes using 6 L/min from a medical air supply. The filter was changed every minute until 20 filters had been collected, and the commencement of sputter was noted. Aerosol deposited on the filter was analyzed using high performance liquid chromatography. The tests were repeated using budesonide inhalation suspension (BIS; 0.25 mg/2 mL, Pulmicort, AstraZeneca). Average fine particle fraction (FPF; % of particles $< 4.7\ \mu$m) for each drug was measured using a Malvern Spraytec laser particle sizer (Malvern Instruments Ltd). Respirable delivered dose (RDD; mass of particles $< 4.7\ \mu$m) was calculated. Nebulization time was much longer for the AeroEclipse II nebulizer than the LC Sprint, with mean sputter points of 711 and 261 seconds respectively using salbutamol sulphate, and 521 and 285 seconds respectively using BIS. RDD was also much higher for the AeroEclipse II than the LC Sprint nebulizer, with measures of 818 and 480 μg respectively using BIS. A small sample size was used for this study, so further testing is required to substantiate these preliminary findings. Comparative testing of different types of nebulizer with child and adult breathing patterns and different drug formulations may provide useful information to inform prescribing decisions.

67. NASAL DEPOSITION ANALYSIS OF A NANO-IN-MICROPARTICLE VACCINE FORMULATION IN CHILDREN AND ADULTS USING CAST MODELS

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Summary

Vaccination is undoubtedly one of the most successful inventions in medical history. But today the number of people refusing vaccines is increasing mainly in developed countries. Avoiding syringe and needle by using alternative administration routes is one opportunity to tackle this issue. For this purpose nasal administration of powder vaccine formulations offers some great advantages. Nasal drug delivery is non-invasive, well accepted and with respect to vaccines it leads to a better immunisation especially in younger patients. In this work a nano-in-microparticle (NiM) vaccine formulation was prepared and analysed with respect to its deposition profile in a child's and an adult's nose by using two nasal cast models (from Boehringer Ingelheim) with and without mimicked inspiration. Nanoparticles were achieved via ionic coacervation of chitosan and sodium deoxycholate. Bovine serum albumin was used as model antigen and was encapsulated in the nanoparticles. To obtain a dry powder NiM formulation the nanosuspension was spray dried using mannitol as matrix. Physical and chemical stability of the nanoparticles is unaffected by the spray drying process. The final formulation was administered with a device for nasal powder application (Powder UDS, Aptar Pharma). The studies show that the amount of vaccine formulation which is deposited in the desired regions (entire nasal cavity without nostrils) as well as the distribution within the nasal cavity differs between adult and child. Nasal deposition averaged 83.5% (of the delivered dose) without air flow and 72.4% with air flow for the adult's model; for the child's nose, it averaged 79.5% and 74.2%, respectively. For both models the amount of vaccine that has been deposited in the desired regions was higher without simulated inspiration. Application without inspiration is probably also easier to perform for patients and healthcare staff.

68. IMPROVING NASAL DRUG DELIVERY AND MEETING PATIENT PREFERENCES WITH HFA NASAL AEROSOLS

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The nasal cavity is ideal for drug delivery for local action and systemic action, due to the relatively large surface area, mucosal surface and blood supply.

Following the Montreal Protocol, as aqueous nasal products were available, CFC nasal products were phased out immediately despite having approximately 50% of the market. Since then, the aqueous nasal spray has dominated the marketplace, but FDA approvals in 2012 for HFA nasal aerosols (Zetonna™, QNASL®) provide alternatives for the 7.8% of US population aged 18 and over, and potentially the estimated 400 million people worldwide, suffering from allergic rhinitis.

Relative benefits of HFA nasal aerosols compared to aqueous nasal sprays are demonstrated via clinical studies quantifying initial deposition by gamma scintigraphy of 2 different nasal devices/formulations containing the same active ingredient: ciclesonide HFA nasal aerosol (74 μg/actuation) and ciclesonide aqueous nasal spray (50 μg/actuation, Omnaris®) in an open label, single dose, single site, non-randomised study. Delivery via HFA nasal aerosol resulted in deposition of almost the entire delivered dose within the nasal cavity (mean 98.4% vs. 76.4% for aqueous), negligible external nasal drip (0.0% vs. 22.7% for aqueous), negligible lung deposition (1.4%) and minimal deposition in the nasopharynx (0.2%).

The improved deposition and retention of the HFA nasal aerosol compared to the aqueous nasal spray (from this and other published studies), with less dripping down the nose and less drainage down the throat (meaning no aftertaste or odour) are advantageous, in line with preferences desired by patients.

69. COMPARISON OF IMPACTION AND NON-IMPACTION METHODS FOR MEASURING SPRAY PATTERNS FROM MDIs

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This paper presents a comparison of impaction and non-impaction spray pattern methods as recommended by the U.S. FDA in a recently published draft guidance describing *in vitro* tests for establishing bioequivalence (BE) of test and reference metered dose inhalers (MDIs) containing albuterol sulfate [1]. The spray pattern results for both methods were collected at 3 cm from the MDI actuator mouthpiece edge from albuterol sulfate MDI product samples using an automated actuation system with parameters derived from a previously conducted QbD-based usage study of trained testers within the product's targeted patient population as recommended by the U.S. FDA [2]. The impaction and non-impaction measurements were collected using a fax paper method and the Proveris SprayVIEW® NMDI instrument respectively. Results include: 1) comparisons of spray pattern Dmin, Dmax, and Ovality (ratio of Dmax to Dmin) measurements for each method; 2) spray pattern area measurements for the non-impaction method according to FDA recommendations [1],[2]; and 3) high-speed laser illuminated videos of the aerosol plume impacting the fax paper surface. Qualitative images and the ovality ratio results confirmed that the methods produced similarly shaped spray patterns. However, the impaction method results showed significantly more variability, with smaller reported Dmin and Dmax values, than the non-impaction results. The high-speed laser illuminated videos showed a significant amount of particle bounce from the fax paper surface and the clear formation of the normally ''free-jet'' plume transforming into a ''wall-jet'' plume due to the surface's presence – both consistent with the smaller reported spray pattern results.

70. SYSTEM TO PERFORM FLOW PROFILE MEASUREMENTS WITH INHALATION DEVICES WHILE USED BY HUMAN VOLUNTEERS

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Flow profile studies are not explicitly mentioned in the OIP guideline [1], although most clinical development plans for generic dry powder inhalers (DPI) carefully enquire this aspect and its results. The reason is that the guideline implies the need for a study measuring inspiratory flow profiles.

For the lack of a commercially available measuring device, Inamed developed a system according to several criteria.

The system was set up from components, which are commercially available and calibrated in a way that it allows to measure the pressure drop at the mouth piece of an inhaler as a function of time. The data had to be collected and converted into a flow rate as a subject inhales through a dry powder inhaler. The modification of the DPI does not alter the airflow resistance of the inhaler. The data is analysed for typical parameters like peak inspiratory flow rate or inhaled volume to generate output parameters for characterisation and comparison of the inhalation.

Based on a thorough validation and qualification our system has proven to be reliable in 4 clinical trials, with more than 400 patients. It has been used with various DPIs amongst them were Turbohaler and Diskus as well as one breath triggered device.

The system can be used for both drug free studies with focus on the device and the handling itself or for studies with a drug delivery to the patient. Additionally this can be in combination with pk and scintigraphic deposition studies.

71. THE ORBITAL®: A NOVEL HIGH PAYLOAD MULTI-BREATH DRY POWDER INHALER

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Background: The Orbital dry powder inhaler (DPI) is a novel dry powder inhaler designed to deliver high-doses of

drugs to the respiratory tract in a single dosing unit via multiple inhalation maneuvers.

Methods and Results: The Orbital DPI was tested in its prototype configuration with the full payload contained in a single dosing unit (the 'puck') and compared to a conventional RS01 (Plastiape S.p.A.) capsule device where the payload was divided over 10 capsules used sequentially. Two formulations were evaluated: 200 mg spray-dried ciprofloxacin and 200 mg spray-dried mannitol. The systems were evaluated for their physico-chemical properties and aerosolisation. The particulate systems had different morphology, thermal response, moisture sorption and stability; however, they had similar aerodynamic sizes making them suitable for comparison with both devices. The aerosolisation performance from the Orbital DPI and RS01 was dependent upon the formulation type; however, the fine particle fraction (FPF) produced by the Orbital DPI was higher than the RS01. The FPF for ciprofloxacin and mannitol were $67.1 \pm 1.8\%$ and $47.1 \pm 2.2\%$, respectively.

Conclusions: The Orbital DPI provides a means of delivering high doses of dry powder to the respiratory tract through multiple breath maneuvers from a single reservoir of powder. This approach allows the delivery of a wide range of high-pay load formulations (>100 mg) for the treatment of a variety of lung disorders with much reduced handling by the patient.

72. *IN VITRO* STUDY OF AEROSOL DEPOSITION IN NASAL CAVITIES DURING INHALATION AND EXHALATION

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Summary

The aim of this work is to study the influence of the particle size and the air flow rate during inhalation and exhalation process on nasal aerosol deposition. In order to carry out this cartography, a nasal cast model was built from epoxy plastic based on CT-scans. The nasal cast can be dismantled in 4 parts and the aerosol deposition into the different region (nose, nasal valve, turbinate, maxillary, ethmoidal and frontal sinuses, sphenoid and nasopharynx) was measured. Three different aerosol sizes (Volume Median Diameter (VMD) from 1.1 μm to 9.8 μm) were generated by nebulization and three different air flow rates were applied on the nasal cast during inhalation and exhalation process (from 2 L/min to 90 L/min).

Statistical analysis was performed to evaluate the correlation between the deposited mass and the VMD and the air flow rate. Results have shown an influence of VMD and air flow rate on deposited aerosols on the turbinates, on the nasopharynx and on the total deposited mass in the nasal model during inhalation and exhalation process. For the nose and the nasal valve the correlation was found between the deposited mass and the VMD during inhalation. While during the exhalation it depends on both the VMD and the air flow rate.

For maxillary, sphenoidal and ethmoidal sinuses no significant correlation between the deposited mass and the tested parameters was determined.

For the frontal sinus no mass was detected in both inhalation and exhalation process and then no correlation could be determined with the two tested parameters.

73. MODELLING OF *IN VITRO* DEPOSITION OF RESPIRABLE POWDER FORMULATIONS USING ARTIFICIAL NEURAL NETWORKS

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Summary

Cascade impactors are used to study the *in vitro* deposition of aerosol products and are accepted worldwide by regulatory bodies, such as the United States Federal Drug Administration, as a means of comparing the bioequivalence between products. They are also employed in general research and development activities. The method of calculating aerosol parameters from measurements in these apparatus is prone to operator error and collection of the drug deposited can be time consuming. The purpose of this study is to determine the feasibility of using artificial neural networks (ANN) to predict aerosol deposition using different formulations and device characteristics. Published data[1] was used to train and test the ANN using fine particle fraction (%) as the dependent variable. Unscrambler™ was used to minimise the number of descriptors in the input vector, by removing fields that did not contribute significantly to explaining the variance in the dataset. The significant descriptors were combined to form an input vector that was used to search the predefined ANNs in the Neurosolution software™ and to identify the optimum architecture. A multilayer perceptron proved the best architecture for this data set by producing high R^2 value for training (0.99), cross validation (0.99) and test set (0.96) and low errors between the desired output and the output generated from the ANN. In conclusion, this pilot study showed that ANN is a promising technique, and could be readily applied to large, diverse datasets to generate a robust and predictive model capable of predicting a cascade impactor output.

74. EFFICIENCY OF VALVED HOLDING CHAMBERS: NUMERICAL COMPARISON STUDY AT CONSTANT FLOW

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Not all patients have the capacity to properly use a pressurized Metered-Dose Inhaler (pMDI) due to the need to breath-hand coordination. The Valved Holding Chamber

(VHC) devices extend the distance between the pMDI and the patient's mouth. They also contribute to the reduction of the oral pharyngeal spray deposition and allow the patient to breathe normally. The main objective of this work is to numerically evaluate various VHC devices commercially available in terms of mass deposition. Through the use of Computational Fluid Dynamics (CFD) the airflow velocity and turbulence fields were calculated for four geometries (i.e. A2A, Aerochamber, NebuChamber and Volumatic). The airflow fields at 30 L/min allowed the prediction of pMDI drug particle deposition in different zones of the geometry. The evaluation of VHC's efficiency was done by calculating the different mass deposition fractions for each geometry zone, as well as, the exit Fine Particle Dose (FPD) and Mass Median Aerodynamic Diameter (MMAD). The results show that the Volumatic has the highest body deposition, while the NebuChamber presents the highest USP throat value. The Aerochamber shows the higher valve deposition value. A2A has a lower USP deposition but a high body deposition. Regarding the amount of drug reaching the Cascade Impactor (CI), the Aerochamber presents the best result, as well as, the highest amount of FPD delivered. Meanwhile, the Volumatic has the lowest MMAD value delivered but the worst FPD result. Based on the results, the Aerochamber presents higher FPD available to the CI/lungs.

75. MEASUREMENT METHODOLOGIES FOR THE DETERMINATION OF ELECTROSTATIC PROPERTIES OF PARTICLES FOR INHALATION

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The accumulation of electrostatic charge on a dry powder inhaler (DPI) formulation occurs both during manufacturing and upon de-agglomeration of the delivered dose via an inhaler device. Researchers have sought to understand this complex phenomenon to determine whether the build of charge is a critical factor which may contribute to the overall performance. Conventional net charge measurements of bulk powders are normally performed with a Faraday pail; however, there are issues with introducing samples to the pail as additional triboelectrification may occur during sample transfer. Furthermore, a Faraday pail does not take into account the bipolar nature of the charges present and therefore may not be a useful tool for measuring charge build up on the respirable particles produced post aerosolisation of a DPI dose. The authors present a novel method to introduce powder samples to a Faraday pail to provide accurate net charge measurements of bulk powder samples post processing steps. Furthermore, the authors have used the bipolar Next Generation Impactor (bp-NGI), as introduced at DDL 23, in conjunction with a flow through Faraday pail (FTF) to determine the effect of humidity on the net charge build up on the device and capsule and the bipolar charge to mass ratios (Q/m) of respirable DPI particles.

76. VALIDATION OF A GENERAL *IN VITRO* APPROACH FOR PREDICTION OF TOTAL LUNG DEPOSITION IN HEALTHY ADULTS FOR PHARMACEUTICAL INHALATION PRODUCTS

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Background: A validated method to predict lung deposition for inhaled medication from *in vitro* data is lacking in spite of many attempts to correlate *in vitro* and *in vivo* outcomes. By using an *in vivo* like *in vitro* set up and analysing inhalers from the same batches both *in vitro* and *in vivo* we wanted to create a situation where information from the *in vitro* and *in vivo* outcomes could be analyzed at the same time.

Method: Nine inhalation products containing either budesonide or AZD4818 were evaluated. These comprised two pMDIs, a pMDI plus a spacer, four DPIs and two dosimetric nebulisers. *In vitro*, an *in vivo* like set up consisting of anatomically correct inlet throats were linked to a flow system that could reply actual inhalation flow profiles through the throat to a filter or to an impactor. *In vivo*, total lung deposition was measured in healthy adults by pharmacokinetic methods.

Results and conclusion: We could show that the amount of drug escaping filtration in a realistic throat model under realistic delivery conditions predicts the typical total lung deposition in trained healthy adult subjects in the absence of significant exhaled mass. We could further show that by using combinations of throat models and flow profiles that represent realistic deviations from the typical case, variations in ex-cast deposition reflect between-subject variation in lung deposition. Further, we have demonstrated that ex-cast deposition collected either by a simple filter or by a cascade impactor operated at a fixed flow rate using a mixing inlet, to accommodate a variable flow profile trough the inhaler, equally well predict the lung deposited dose. Additionally, the ex-cast particle size distribution measured by this method may be relevant for predicting exhaled fraction and regional lung deposition by computational models.

77. FLUOROCHEMICAL MEDIATED PHASE TRANSFORMATIONS OF BECLOMETHASONE DIPROPIONATE

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Summary

Isothermal calorimetry is a suitable technique to investigate fluorochemical mediated phase transformations that mimic propellant systems in metered dose inhalers. The early stages of beclomethasone diproprionate (BDP) clathrate formation with using a surrogate propellant (decafluoropentane-HPFP) was measured with isothermal calorimetry. Particles were

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taken from the isothermal system (TAM) and subject to traditional thermoanalysis to support the clathrate formation hypothesis. Differential scanning calorimetry (DSC) thermograms elicited a decreased onset temperature for crystallisation for each consecutive cycle of perfusion. Thermogravimetric analysis (TGA) analysis demonstrated the embedding of the HPFP moiety within the BDP framework through mass loss proportional to the time spent under elution with HPFP. Fourier Transform Infrared Spectroscopy (FTIR) shows a gradual change in the molecular vibrations as a function of perfusion time with HPFP, yet confirms the bulk of the particles to be characteristic of BDP. This work thus establishes isothermal calorimetry as a useful diagnostic tool in predicting stability in hydrofluoroalkane (HFA) formulations.

78. DISTILLING KEY INFORMATION ON THE EFFICACY OF PULMONARY DRUG DELIVERY FROM PHARMACOKINETIC (PK) AND PHARMACODYNAMIC (PD) STUDIES

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In its native form, the pharmacokinetic (PK) profile of blood (or plasma) concentrations simply represents the systemic exposure of a drug. This is of paramount importance in understanding the magnitude of likely side effects of inhaled drugs intended for local action in the lung, or the efficacy of inhaled systemically-acting drugs. The key parameters used to characterise the PK profiles after dosing via other non-parenteral routes, e.g. oral dosing, such as the maximum observed blood concentration (C_{max}), the time taken to achieve the maximum concentration (t_{max}), the area under the blood concentration-time profile (AUC) and the time taken for blood concentrations to decline by a half ($t_{1/2}$), after the maximum concentration, may all be influenced by the bioavailability of the drug (i.e. its rate and extent of absorption. For inhaled medicinal products, these PK parameters are usually reflective of the disparate absorption characteristics from the different sites of deposition which result after inhalation. Thus the interpretation of changes, or a lack of anticipated changes, in C_{max}, t_{max} and AUC requires careful dissecting of the data and a review of the sensitivity of the measured parameters to changes in the deposition pattern and consequent absorption profile of the drug. There are numerous complexities in interpreting PK blood concentration data profiles from studies of orally inhaled medicinal products. The distillation of PK data to provide key summary information is not a single process with universal applicability but one which warrants bespoke modification, giving due consideration to the study objectives.

79. EFFECT OF PROCESS PARAMETERS AND POWDER PROPERTIES ON LOW DOSE DOSATOR CAPSULE FILLING

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Summary

The aim of the present work is to identify and understand the complex relationship between powder properties and the capsule filling performance of a dosator nozzle machine. Twelve different powders, mainly inhalation carriers and selected APIs, were characterized and filled into size 3 capsules following a screening DoE for different process parameters. Subsequent multivariate statistical analysis was used to identify the influence of various powder properties and process parameters on the capsule net weight and weight variability. There was a clear correlation between the dosator filling performance the dosator diameter, dosing chamber, powder layer and the powder densities. Moreover, wall friction angle and Basic Flowability Energy are also significant parameters. The results were used to develop a predictive model for the process and furthermore a Design Space for the different nozzles and powders.

The results of the work will translate into guidelines for improving the current design of capsule filling equipment, for particle engineering and ultimately will allow the manufacturing of inhalation products with desired quality attributes. This study is the first scientific qualification of dosator nozzles for low fill weight (5–45 mg) capsule filling.

80. THE INTERPLAY BETWEEN VARIABLES IN THE FORMULATION AND DISPERSION OF ADHESIVE MIXTURES FOR INHALATION

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An insufficient understanding of (statistical) interactions between variables in the formulation and dispersion of adhesive mixtures for inhalation leads to a low utility of studies concerning these processes. Drug detachment from lactose carriers is described in a basic manner to improve the understanding of the interplay between variables. It is suggested that the effect of any variable on drug detachment depends on how it alters the so-called energy ratio distribution during inhalation and on the initially detached drug fraction. Therefore, interactions between the effects of component and process variables on the detached drug fraction and any inhalation variable that alters the initially detached drug fraction (e.g. inhalation flow rate) are always to be expected. In addition, interactions between variables arise if one variable affects the way in which another variable alters the energy ratio distribution. This may occur if these variables have a non-additive effect on drug detachment through the same so-called 'principal factor(s)' of the mixture, or if one variable affects the relevance to drug detachment of changes in the principal factors that are caused by another. It follows that multi-order interactions between variables are very likely to occur. Anticipating these interactions will increase the utility of future studies and the efficacy of quality by design approaches to the development of dry powder inhalation products.