Nebulising Nicotine: An Old Drug Gets a Makeover

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Health risks associated with tobacco have a long history. John Hill in 1761 first wrote of the risks of cancer of the lip associated with pipe smoking. In Germany in the 1920s and 30s informal case control studies showed an overwhelming association between smoking and lung cancer. In Nazi Germany before and during WW2 there were unsuccessful attempts to eradicate smoking. These risks were rediscovered after WW2 most notably by Doll and Hill in large observational studies that showed clear and strong dose response relationships between smoking and a variety of health problems. Policy and legislation to curb tobacco was slow to develop as was appropriate help for smokers to quit. In the late 1970s AB Leo in Sweden invented the first nicotine replacement in the form of chewing gum. This was followed by a variety of new formulations using oral, nasal and dermal absorption to provide lower but more prolonged plasma nicotine levels than from smoking thus reducing the withdrawal symptoms that are the main drivers of regular smoking. In the 1960s the first e-cigarette concepts were developed vaporizing nicotine rather than burning tobacco, but were never commercially developed. E-cigarettes were rediscovered in the early 2000s and have undergone a number of transformations, becoming very popular amongst a growing number of smokers, but creating considerable controversy in the tobacco control community. Modern e-cigarettes are sophisticated delivery devices. As an alternative therapeutic mode of nicotine delivery for smoking cessation we have developed and built a simple standard nicotine metered dose inhaler (MDI). The inhaler uses nicotine lactate and formulations of 50, 100 and 200 μg/puff.

Bioavailability of nicotine from the MDI is less than from a standard cigarette. An RCT of the nicotine inhaler plus a nicotine patch resulted in a doubling of quit rates at 6 months versus a placebo inhaler and nicotine patch. The inhaler is currently available in the US as an alternative to e-cigarettes. Registration of the MDI as a medicine for smoking cessation in New Zealand is under development. A number of issues regarding registration and possible future developments of nicotine inhalation for smoking cessation will be discussed.
Inhaled Aspirin: An Innovative Solution Against Influenza

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Therapeutic intervention strategies against severe, hospitalized influenza are very limited so far. In this study we've investigated the inhalation of LASAG (D,L-lysine acetylsalicylate · glycine), a compound with a new antiviral mode of action. In cell culture and animal experiments LASAG was found to inhibit the signalling factor NF-kB in the host cell that is essential for replication of influenza viruses.

In a randomized, double blind, parallel group, placebo controlled study we administered aerosolized LASAG (800mg equivalent to 400 mg ASA) three times daily in adult hospitalized patients with acute serious influenza. The LASAG was delivered as an aqueous solution with an innovative inhalation system, AKITA Jet (Vectura Ltd., Chippenham, UK). This system allows a high and reproducible lung deposition by breath controlled inhalation. The primary objective of this study was to evaluate the clinical efficacy of aerosolized LASAG vs. placebo added to standard of care treatment.

A total of 41 patients (24 LASAG; 17 placebo) finished the study per rotocol. Patients with severe influenza as indicated by high composite symptom scores (CSS) ≥ 14 in validated influenza symptom questionnaires showed significantly reduced time to alleviation of their symptoms when treated with LASAG compared to placebo (38.3 hrs vs. 56.2 hrs; Satterthwaite t-test p=0.0365). The secondary endpoint alleviation of clinical signs was also significantly improved in the LASAG group compared to placebo.

This is the first clinical demonstration of the use of a host-cell signalling inhibitor that does not directly target viral structures as an efficient antiviral drug. The drug was administered to the airways of the patients by aerosol inhalation. Time to alleviation of symptoms as well as clinical signs could be reduced significantly in hospitalized patients with severe influenza.
Comparative Studies of The Pharmacokinetics And Tissue Distribution Of Propylene Glycol In Rat by Inhalation And Intracheal Instillation

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Objective: To compare the difference of pharmacokinetics and distribution of Propylene glycol (PG) in rat by inhalation and intratracheal instillation.

Methods: Aerosolized PG was generated by a home-made capillary aerosol generator (CAG) and conducted to nose-only chambers. The targeted delivery dose of 500 mg/kg was achieved by exposure to 29.8 mg/L aerosol for 26 min. By intratracheal route, rats received 300 µL of 30 % PG solution using a IA-1B-2 inches-Microsprayer (PennCentury, Philadelphia, PA). Plasma samples were collected from 3 rats/sex/group at the following time points: pre-exposure, mid-exposure (intratracheal instillation not included), end-of-exposure, and 30 min, 60 min, 120 min, 240 min, 480 min, 1440 min post-exposure after inhalation exposure and intratracheal instillation. Tissue (lung, liver, kidney) samples were collected from 3 rats/sex/group at the following time points: mid-exposure (intratracheal instillation not included), end-of-exposure, and 30 min (inhalation exposure not included), 60 min and 240 min post-exposure after inhalation exposure and intratracheal instillation. A validated GC-MS bioanalytical method was used to determine the PG concentrations in plasma and tissues. The LLOQ is 1μg/mL.

Results: The CAG-generated PG aerosol had a mass median aerodynamic diameter (MMAD) of 1.56 μm, with a 1.37 geometric standard deviation (GSD). The pharmacokinetics parameters: tmax=31min, Cmax = 452.933, AUC(0-t)=54361.1, AUC(0-∞)=55431.397, t1/2=108.818 min for inhalation exposure; tmax=2min, Cmax=756.767, AUC(0-t)=46222.517, AUC(0-∞)=46302.999, t1/2=79.353 min for intratracheal instillation. The inhalation- instillation dose ratio was 1.29 (500/387 mg/kg), and the AUC(0-t) ratio was 1.17. There no differences of PG concentrations in the lung, liver and kidney between inhalation and intratracheal routes, and no differences of the PG distribution among the 3 tissues. Conclusion: PG in plasma and tissues reached maximum at the end of inhalation exposure and intratracheal instillation, but intratracheal instillation was higher than inhalation exposure. The AUC(0-t) of inhalation exposure was close to that of intratracheal instillation. PG in plasma and tissue became decline after inhalation and intratracheal instillation. PG has no tissue specificity among lung, liver, and kidney. Our studies may provide support for toxicological assessment of propylene glycol aerosol.
L1.2

_Inhaled Cannabis: The New Frontier_

Andrew Loxley

Andanase – Belgium

AWAITING ABSTRACT
Critical Physicochemical Attributes Of Polymeric Nanoparticles In Pulmonary Drug Delivery For Tuberculosis Treatment

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Nanoparticulate delivery system has received a widespread interest for use to deliver therapeutics for treatment of different diseases such as cancer and infection. Nanomaterials enable therapeutic agents to be delivered in a targeted fashion. Nanoparticles improve drug solubility, extend drug half-life, improve therapeutic index, and reduce drug immunogenicity. The nanoparticles can penetrate the mucus barrier and biological interface to raise the drug bioavailability.

With reference to lung tuberculosis, delivering nanoparticles via the lung gains much interests as nano-size particles can cross the cellular barrier. The nanoparticles can be designed to be taken up by macrophages for delivery of drugs directly to tubercle bacilli and thus treating the disease effectively. However, nanoparticles have the disadvantages of being exhaled from lungs after pulmonary administration. The inhaled particles should have an aerodynamic diameter between 1 and 5 µm in order to enable the drugs being deposited in the deep lungs. Several approaches have been developed to form nanoparticles with suitable aerodynamic diameters for lung delivery, namely nanoagglomeration, nanocomposite formation and microencapsulation. The current approaches of producing inhalable nanoparticles have several drawbacks. Firstly, they require meticulous efforts in the formulation steps. Each formulation is only likely to be applicable to a specific nanoparticle type. The microscale particles are known to face issues of poor flowability and dispersibility in association with their cohesive nature. The microencapsulated dosage forms run the risks of inadequate nanoparticle release. The nanoparticle size can change during the microencapsulation process, suggesting the size-dependent biological performances of nanoparticles can be affected by nano-to-micro scale transformation.

This presentation highlights physical blending using microcarrier as the alternative approach to deliver polymeric nanoparticles via the pulmonary route. The critical physicochemical parameters of nanoparticles and microcarrier that are required for pulmonary inhalation are identified. The design of nanoparticles that are essential for intracellular trafficking by macrophages, as well as, the influences of nanoparticles on drug migration from the extracellular into the cytoplasmic compartment of macrophages will be discussed.
Sustained-Release Formulation Of Salmon Calcitonin For Inhalation Prepared With Fine Droplet Drying (FDD) Process

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Salmon calcitonin (sCT) inhibits calcium resorption from bones and is used for the treatment of osteoporosis and hypercalcemia. Parenteral routes such as intramuscular injection are used for the administration of sCT due to the poor oral absorption and stability in the gastrointestinal tract. Inhalable powder is an attractive alternative to injectable formulation. A new powderization technology employing the inkjet head, defined as the fine droplet drying (FDD) process, was applied to obtain uniform fine particles. Poly (lactic-co-glycolic) acid (PLGA) with an average molecular weight of 10 kDa (Resomer® RG502H) was used as a carrier to prepare sustained-release (SR) formulation of sCT (sCT/SR) with prolonged systemic biological action. An FDD process using RICOH MH2420 was used for the preparation of uniform fine particles. For preparing the respirable powder (RP) formulation of sCT/SR (sCT/SR-RP), the fine particles of sCT/SR were mixed with lactose carrier (Respitose® SV003). The prepared RP formulation was characterized in terms of physicochemical and in vitro inhalation properties. After the insufflation of sCT samples (40 μg-sCT/kg), hypocalcemic effect of sCT was evaluated in rats. The average particle size of sCT/SR was found to be 3.6 μm. The structural changes of sCT were evaluated by thioflavin T (ThT) binding assay for detection of β-sheet structure. In ThT binding assay, no significant aggregation of sCT was observed in sCT/SR, possibly leading to conservation of biological effect. According to the release profiles of sCT samples in the simulated lung fluid, the sCT release behavior showed biphasic pattern with initial burst and slow diffusion. In the second phase, the sustained drug release might be attributable to drug diffusion from PLGA matrix and matrix erosion mechanisms, indicating encapsulation of sCT in PLGA particles.

The prolonged release profile of sCT from sCT/SR particles might result in enhanced efficacy of action after intratracheal administration of sCT/SR. On the basis of the results from cascade impaction analysis on sCT/SR-RP, the fine particle fraction value was estimated to be 28%, suggesting that sCT/SR-RP showed fine inhalation property. After the insufflation of sCT-RP and sCT/SR-RP (40 μg-sCT/kg) in rats, the area under the plasma calcium levels-time curve were decreased by 8% and 35%, respectively, compared with control-RP group. Due to the sustained drug release from PLGA particles, sCT/SR-RP could enhance the hypercalcemic effect of sCT. From these observations, the strategic application of FDD process could be efficacious option to prepare inhalable formulation of calcitonin, as well as other therapeutic peptides and proteins, to enhance their therapeutic potential.
Synthetic KL4 Peptide As An Effective siRNA Carrier For Pulmonary Delivery

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Pulmonary delivery of the siRNA has great potential for the treatment of many lung diseases. However, many non-viral delivery systems currently being investigated are either too toxic for clinical use or with low efficiency in vivo. Thus, a vector with high efficacy and good safety profile for pulmonary siRNA delivery is a major problem that needs to be addressed. KL4 is a 21-residue peptide containing hydrophobic leucine interspersed with cationic lysine (KLLLLKLLLLKLLLLKLLLLK-NH2). This synthetic peptide is an active component in a pulmonary surfactant product Surfaxin, which is a FDA approved intratracheal suspension to prevent respiratory distress syndrome in premature infants. KL4 is structurally similar to pulmonary surfactant protein B (SP-B) and designed to imitate the function of SP-B. The safety and the cationic nature of the KL4 makes it a potential candidate for siRNA delivery. The aim of this study was to explore the potential of KL4 as a vector for pulmonary siRNA delivery. The physicochemical properties such as binding affinity, particle size and morphology of KL4/siRNA complexes were characterized. The transfection efficiency and cytotoxicity of the KL4 system were carried out on lung epithelial cells. Agarose gel retardation assay was used to study the siRNA binding affinity of the KL4 peptide. Complete binding was observed at ratio 20:1 (w/w) and above. The hydrodynamic size of the KL4/siRNA complexes at different ratios were analyzed by dynamic light scattering. The particle size distribution was large, indicating that aggregates might be present due to the hydrophobic nature of the KL4 peptide. The morphology of the KL4/siRNA complexes were visualized under transmission electron microscope (TEM). The size of the complexes became smaller as the peptide to siRNA ratio increased. Two human lung epithelial cell lines, A549 cells (lung adenocarcinoma) and BEAS-2B cells (bronchial epithelial cells), were used to evaluate the GAPDH siRNA transfection efficiency of KL4. Western blotting assay was used for measuring the GAPDH protein expression level. The gene silencing efficacy on A549 cells improved as the peptide to siRNA ratio increased, reaching more than 60% of knockdown at 30:1 (w/w) ratio. Significant knockdown of GPADH protein (~80%) was detected at the ratio 30:1 (w/w) on BEAS-2B cells compared with Lipofectamine 2000 (~50%). MTT (3-(4, 5-dimethylthiazolyl-2), 5-diphenyltetrazolium bromide) assay was used to assess the cytotoxicity of the KL4/siRNA complexes. Both the A549 and BEAS-2B cells were treated with the complexes from 5:1 to 30:1 weight ratios.
How Its Made – Inhalable Nucleic Acid Powders

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The discovery of RNA interference (RNAi) has been drawing attentions as a promising new strategy to treat diseases, especially those that are deemed difficult to manage due to limited drug-able targets. Short interfering RNA (siRNA) is a small non-coding RNA that utilizes RNAi to silence gene expression. Pulmonary delivery is a desirable route of administration for siRNAs for the treatment of lung diseases such as asthma or respiratory infections, with several animal and clinical studies demonstrating favorable results. Based on these findings, the current study aimed to develop an inhalable dry powder formulation of siRNAs using spray drying technology, a production method that can be scaled up relatively easily. Under a predetermined spray drying condition, siRNA was formulated into dry powder in its naked form (in the absence of delivery vectors or protectants) at 0.75% or 2% by weight, with mannitol as the bulking agent. The yield of production was around 70% (compared to the initial mass input). The integrity of the siRNAs after spray drying was evaluated using both gel retardation assay and liquid chromatography. The results suggested that the structure of siRNA remained intact with no detectable degradation after spray drying. The physical diameter of the powder was measured using laser diffractometry. At 0.75% w/w siRNA, the powder has an average median diameter of 5.2 µm, which increased to 8.0 µm when the siRNA load was increased to 2% w/w. The aerodynamic profile of the powder was studied using the Next Generation Impactor (NGI) in accordance to the pharmacopoeial protocol. When coupled with a low resistance inhaler (Osmohaler®/Breezhaler®), the 0.75% w/w siRNA powder formulation demonstrated a fine particle fraction (FPF) of 55%, which is considered satisfactory among commercially available dry powder inhalers (DPIs). However, the FPF reduced to 17% for the 2% w/w formulations. As a proof-of-concept, the aerosolizing properties of these powders were improved by either bovine serum albumin (BSA) or l-leucine. For the 0.75% w/w siRNA formulation, incorporating BSA at 10% w/w improved FPF to 61%, whereas 50% w/w l-leucine drastically improved FPF of the 2% w/w siRNA formulation to 44%. Importantly, these modifiers did not form complexes with siRNAs. In conclusion, inhalable dry powder of naked siRNAs up to 2% w/w were prepared using spray drying technology. The integrity of siRNAs remained intact after formulation. The respirable fractions achieved were above 40%.
Comparative In-Vitro And In-Vivo Performance Of Fluticasone Propionate Pressurized Metered Dose Inhaler (pMDI) With Aerochamber Plus®Spacer

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Pressurized metered dose inhaler (pMDI) is one of the most commonly use dosage forms for respiratory disease such as asthma and COPD. It is crucial that an appropriate technique should be addressed for dosing the inhaler in order to ensure sufficient drugs are delivered and deposited into the lung. However, it is sometimes not easy for patients to use, typically for elders and children, therefore add-on devices like mask and spacer are developed. They help patients to use inhaler easier and more convenient. Aerochamber Plus® is a spacer commonly used in different commercial inhalers. This study demonstrated the in vitro and in-vivo comparison between pMDI with and without Aerochamber Plus® spacer by using Fluticasone Propionate pMDI. Both commercial product Flixotide® and our developing generic (FLU076071) are used for the testing. Aerodynamic particle size distribution (APSD) measurement is conducted for in-vitro assessment, parameters included fine particle mass (FPM), fine particle fraction (FPF), mass medium aerodynamic diameter (MMAD) and geometric size deviation (GSD) are analyzed. In addition, an open-label, randomized, single dose, crossover study is conducted in eleven healthy volunteers with a mean age of 30 ± 4.5 years for evaluation. Flixotide®, FLU076071 and FLU076071 with Aerochamber Plus® are studied. AUC0-t, AUC0-∞ and Cmax are the parameters used to assess bioavailability. In vitro data show that FPM decreases 21% in both Flixotide® and FLU076071 with Aerochamber Plus® spacer, compared to data without spacer, despite FPF is similar in all inhalers with or without spacer. MMAD and GSD are slightly lower in both products with spacer. On the other hand, in-vivo PK data show that AUC0-t is 1264.1 ± 804.6 (pg×h/mL), AUC0-∞ is 1583.4 ± 948.4 (pg×h/mL) and Cmax is 149.058 ± 86.976 (pg/mL) for reference drug (Flixotide®), while for test drug (FLU076071), AUC0-t is 1295.8 ± 766.8 (pg×h/mL), AUC0-∞ is 1748.7 ± 900.9 (pg×h/mL) and Cmax is 142.212 ± 65.911 (pg/mL). Test product show highly similarity to reference product (T/R point estimate: 0.99 for AUC0-t, 1.01 for Cmax), but cannot demonstrate bioequivalence with each other due to limited sample size. In addition, the PK data of test drug with Aerochamber Plus® are also evaluated, AUC0-t is 5363.4 ± 2294.7 (pg×h/mL), AUC0-∞ is 7440.4 ± 3460.0 (pg×h/mL) and Cmax is 418.927 ± 159.713 (pg/mL). It is 5 fold higher in AUC and 3 fold higher in Cmax than both reference drug and test drug without spacer used.
**Cyclosporine A-Loaded Nano-Matrix Particle Prepared With Multi-Inlet Vortex Mixer For The Treatment Of Airway Inflammatory Diseases**

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Cyclosporine A (CsA) is currently used as an immunosuppressant for prevention of allograft rejection and treatment of various autoimmune diseases. There have been a number of reports on the application of CsA to the treatment of airway inflammation and chronic asthma. However, the clinical application of CsA to the treatment of respiratory diseases is limited due to the severe side effects evoked by excessive systemic exposure of CsA. In the present study, inhalable nano-matrix particle of CsA with mannitol (nCsAm) was developed using multi-inlet vortex mixer to provide a local pharmacological action of CsA in airways with reduced risk of systemic side effects. A nano-suspension of CsA was prepared by a flash nano-precipitation method using a four-stream multi-inlet vortex mixer, followed by spray-drying with mannitol as a matrix former to obtain the nCsAm.

In the nCsAm, CsA nano-particles dispersed in mannitol, forming micron-sized aggregates during the spray-drying process. In laser diffraction analysis, mean particle size of the nCsAm was 1.3 µm, CsA in the nCsAm was found to be in an amorphous state by X-ray powder diffraction and differential scanning calorimetry analyses. The nCsAm showed rapid dissolution of CsA in distilled water compared with amorphous CsA. NGI analysis demonstrated fine in vitro inhalation property of nCsAm as evidenced by the fine particle fraction value of 66% (MMAD.8 µm), suggesting that the nCsAm were suitable for inhalation. OVA sensitization by intratracheal administration of respirable powder led to significant airway inflammation in rats.

Intratracheally-administered nCsAm (100 µg-CsA/rat) suppressed antigen-induced inflammatory events in rats and reduction of collagen production in the lung tissue by 63% and 71%, respectively. These results were indicative of the therapeutic potential of nCsAm for treatment of airway inflammatory diseases. The insufflation of nCsAm at a pharmacologically effective dose (100 µg-CsA/rat) significantly decreased systemic exposure of CsA compared with the oral administration of CsA formulation at a nephrotoxic dose (10 mg-CsA/kg) in rats. The tissue distributions of CsA within the side-effect-related organs including liver and kidney were markedly reduced in intratracheally-administered nCsAm by 42- and 47-fold, respectively, suggesting the reduction in the risk of systemic side effects. From these findings, inhalation of nCsAm could be a viable delivery option of CsA for the treatment of airway inflammatory diseases with a better safety margin.
Inhalation Therapy of Traditional Chinese Medicine

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For thousands of years, Traditional Chinese Medicine (TCM) has a long history of being administrated by oral, topical and inhalable forms to treat various diseases and improve the quality of life. In ancient China, TCM often took the form of smokes, steam vapors, medicated pillows and aromatic sachets. Thus, the important therapeutic value of inhalable TCM has long been recognized in clinical practice. However, development and approval of inhalable TCM products is difficult due to their complex mixture of chemical components, and challenging formulation development and quality control measures. Thus, only a few TCM metered-dose inhalers products have been approved by the China Food and Drug Administration (CFDA), and no products have been approved in the form of a dry powder inhaler (DPI) or as dosage forms for nebulization. Through a literature search, thousands of articles in Chinese have reported the off-label use of injectable TCMs via nebulization in Chinese hospitals in the last two decades to treat respiratory disease. However, while most of these clinical reports do involve randomized controlled trials with various patient numbers, they are not sufficient to fully demonstrate the safety and efficacy of nebulized TCMs.

In our previous work, various nanocarriers were used to improve drug disposition in the lung and the treatment effect of TCMs. Compared to micronized or spray-dried powders, the nanocrystals provided superior systemic absorption using less excipients. However, the absorption mechanism of the nanocrystals was still unclear. Herein, we have prepared API nanocrystals with three different sizes (about 200 nm, 500 nm and 1 μm) by wet milling and anti-solvent precipitation methods to study their absorption mechanism. The DSC and XRPD characterizations showed that all three compositions were crystalline in form with similar morphology under TEM. As would be expected, the in vitro dissolution velocity increased with a decrease in size of the nanocrystals. In addition, the penetration study across simulated mucus also demonstrated a size dependent penetration with the smaller nanocrystals having the highest penetration ability. FRET results showed that a subset of the nanocrystals dissolved gradually while others remained intact when incubated with the simulated mucus solution. This study was supported by a Research Grant from University of Macau (MYRG2014-00040-ICMS-QRCM).
**Intranasal Dexmedetomidine For Sedation In Children**

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Dexmedetomidine is a highly specific and selective alpha-2-adrenergic agonist with sedative, anxiolytic and analgesic effects. The sedative effect produced by dexmedetomidine is unique in several ways. At low doses, it produces sedation where the patient is drowsy, but remains arousable and cooperative. On the other hand, when the dose is large enough, it produces deep sedation or even general anaesthesia. The sedation produced mimics our natural stage 2 sleep cycle, as evident from the electroencephalograph. No respiratory depression is observed even when large doses are used. These desirable effects of dexmedetomidine lead to various application in perioperative setting in children. It has been used as premedication prior to induction of anaesthesia, prophylaxis of emergence delirium and as adjunct analgesic in children. The use of dexmedetomidine in children with marginal cardiac and respiratory reserve undergoing invasive procedures has also been described in literature. Other potential roles include sedation in awake craniotomy, anaesthesia adjunct in corrective spinal surgery and ophthalmic surgery. It is also increasingly used in procedural sedation in children. Currently dexmedetomidine is only available as intravenous formulation, which has also been used intranasally in children to produce sedative effects. Increasing researches and studies have revealed that the intranasal dexmedetomidine can be used as an effective premedication prior to anaesthesia to relieve anxiety in children. Its effectiveness is comparable or better than the commonly used midazolam. Moreover, it is also used for procedural sedation in children and it is as effective as the other common sedatives including oral chloral hydrate. The benefit of intranasal dexmedetomidine includes its ease of administration, requires only minimal cooperation from children and avoids the unpleasant bitter taste with administration of oral midazolam and chloral hydrate in children. Unlike intranasal midazolam, its administration is not associated with any unpleasant sensation. In summary dexmedetomidine is a drug with diverse utility with increasing clinical evidence to support its various applications in children during the perioperative period coupled with a remarkable safety profile. There is great potential clinical application for the development of intranasal formulation of dexmedetomidine.
Advent Of Q3-Equivalence Approaches For Generic Aqueous Nasal Suspension Drug Products

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Demonstrating bioequivalence (BE) for nasal suspensions has proved challenging, since drug product performance is a function of the integrated effect of device, particle size of the suspended active pharmaceutical ingredient (API), formulation rheology and patient/device interactions. Nasal suspension drug products consist of API particles suspended in an aqueous system in the presence of a range of different excipients. For suspension nasal products, the API particle size is a key critical material attribute, which will affect emitted API particle size and regional deposition of API in the nose. In addition, the particle size of the API will affect the rate of dissolution and permeability at site of deposition in the nasal epithelium and thereby systemic exposure of the API from the nose. The paucity of validated methods for characterizing API-specific drug particle size and particle size distribution (PSD) in nasal formulations has resulted in limited understanding of the relationship between API PSD, regional deposition in the nasal cavity, dissolution and absorption of the API from the nose. This study investigated the utility of the Morpologi-G3-ID to investigate the particle size distribution (PSD) of API formulated nasal sprays. Rotational rheometry and force to actuation during dose delivery was used to investigate formulation structure. A systematic approach was utilised to develop a robust method for the analysis of the PSD of Mometasone furoate in Nasonex and two test formulations containing API of different particle size specification. The test formulation API PSD suggested that the API may have undergone Ostwald ripening, but showed similar trends in the measured particle size as the as-received API and were distinct from Nasonex. Rheometric measurements were sensitive to variations in the Avicel content and at lower concentration than Nasonex, exhibited different gel-like and shear thinning properties. This was also confirmed by measurement of the force to fire measurements during dose delivery. Together, these analytical methods may facilitate the determination of critical material and process attributes that may affect drug product quality.
A Novel In-Vitro Nasal Drug Delivery Testing Platform: Integration Of Nasal Cell System Into A 3D Printed Nose Model

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Nasal drug delivery has emerged as a promising non-invasive alternative for both local and systemic delivery of drugs due to the large surface area in the nasal cavity, avoidance of first pass metabolism and relatively high blood flow, promoting rapid absorption. However, there are several challenges associated with formulating nasal products including: 1) the efficient mucociliary clearance system that could clear the nasal cavity of any xenobiotics within 30 minutes and 2) the small volume and geometrically complex space of the nasal cavity which limits the doses that can be administered. These aspects highlight the complexity of the administration route and the need for further research into the development of novel nasal formulations for efficient delivery of therapeutics as well as the need for reliable preclinical platform to test and screen potential new nasal formulations. Hence, the study presented will explore the different human nasal cell culture systems (i.e. primary nasal cells and RPMI 2650) that could be used to accurately represent the nasal barrier system and serve as an alternative to in vivo models. Subsequently, the selected air interface cell model will be incorporated into a purposed-build 3D printed cast model of the nose to simultaneously test the deposition and mimic the permeation mechanisms of nasal formulations across the nasal mucosa after a bolus inhalation. The 3D apparatus of the nose model takes the form of the glass expansion chamber with additional housing to incorporate Snapwell inserts for cells and an orifice for insertion of the drug delivery device. Attached to a cascade impactor, the set-up was based on the industry FDA guidance for the testing of nasal aerosols and nasal sprays bioavailability and bioequivalence. This model was validated against the original set-up using commercially available Rhinocort Nasal Spray. The applicability of the model was then tested using several other novel nasal formulations including chitosan nanoparticles and Soluplus® Budesonide powder formulation. The successful integration of a cellular model into a 3D printed modified expansion chamber allows for simultaneous investigation of aerosol deposition and drug permeation that mimic the in vivo processes of nasal delivery.
Role of Nasal Formulation of Vitamin D3 in Prophylaxis and Treatment of Osteoporosis

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Intranasal vitamin D3 has been investigated to stimulate the expression of proteins involved in calcium transport. The active hormonal form of 1, 25-dihydroxyvitamin D is not only needed for optimal calcium absorption, but also exerts an inhibitory effect on PTH synthesis and reduces loss of calcium from bones. Vitamin D3 deficiency, calcium deficiency and hyperparathyroidism are the causes of osteoporosis. Osteoporosis is more common in elderly patients with liver/kidney impairment because Vitamin D3 hydroxylation does not occur effectively thus reducing calcium and serum vitamin D3 levels. This causes increase in parathyroid hormone (PTH) levels which stimulates the production of calcitriol. By this mechanism, serum calcitriol is kept at normal levels at the expense of high serum parathyroid concentration. High Vitamin D3 in the serum causes less PTH synthesis, increases bone mass density of the lumbar spine and hip and thus decreases fracture frequency. Vitamin D3 is a fat-soluble vitamin having a very high logP value of 7 and is not available in solubilized form in the GI fluids for efficient absorption. The available tablet dosage forms do not present the drug in the dissolved state. Moreover, Vitamin D3 faces problems from GIT enzymes like 25(OH)ase which function to inactivate Vitamin D3 to 1,24,25(OH) Vitamin D3 which is lesser in biological activity. CYP 3A4 gut wall enzymes may also affect its absorption. Oral Vitamin D3 exhibits highly variable absorption 60-90%. Thus, an alternative strategy i.e. nasal and pulmonary delivery were explored for overcoming these issues. An ion sensitive in-situ gelling nasal spray formulation was prepared using pectin as gelling agent. The spray was evaluated for globule size, mucoadhesion, and ex-vivo absorption study using goat nasal mucosa. The spray exhibited sustained release for duration of 6 days. Liposomal dry powder inhaler formulation was also prepared and optimized batch consisted of trehalose as cryoprotectant and lactose as carrier. The lyophilized dry powder inhalation powder exhibited 43.5% fine particle fraction, ensuring its deposition in the alveolar region for absorption systemically. Superior pharmacokinetic and pharmacodynamic profile were achieved for both the formulations, whereby the relative bioavailability of the nasal spray and DPI formulation was 1.2 and 1.3 times respectively compared to oral route and higher calcium content present in the plasma was estimated which is necessary for absorption of Vitamin D3 and an estimator for higher chances of its absorption from plasma to bones and can be used for prophylaxis and treatment of Osteoporosis.
Critical Elements To Consider When Developing A Dry Powder Inhaler

Keith Ung

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The effectiveness of aerosol drug delivery to the lungs depends on both the device and drug formulation. Currently, marketed inhalation drug products often deliver no more than 15 – 30% of the packaged dose to the lungs, either due to losses in the inhaler device, or deposition in the patient’s mouth-throat. This poses a significant challenge in the development of inhalation drugs, as it can dictate higher nominal doses in order to compensate for losses, and can result in increased systemic exposure to drugs that are orally bioavailable and, in some instances, increases in local and systemic side effects. For inhalation drugs, improved targeting to the lungs can be achieved through good engineering of inhaler delivery system and drug formulation to reduce deposition in the extrathoracic region losses to negligible levels, thereby maximizing the total dose delivered to the lungs. This topic will examine the development of unit dose blister-based inhaler for deep lung delivery. When developing dry powder inhaler for inhaled medications, four key elements should be considered; (i) drug receptacle, (ii) aerosol engine, (iii) flow resistance, and (iv) inhaler mouthpiece geometry.
Materials qualification for packaging and device components is a critical step in developing high quality, safe and efficacious inhalation and nasal drug combination products. Many orally inhaled and nasal drug product (OINDP) packaging and devices are composed of a variety of materials – plastics, elastomers, metals, glass, electronics, etc., that must protect and not adversely affect the drug formulation, but also be functional so that the formulation is delivered as intended over the shelf life of the product. Packaging and device components must, therefore, serve a variety of diverse purposes. To ensure that materials meet these objectives, qualification processes based on risk management approaches, GMP concepts, good analytical practices, and supply chain quality management are required. This presentation will provide an overview of materials qualification in the drug development process, discuss baseline requirements for materials quality – important for both product developers and suppliers -- and provide case studies related to specific components and final product types.
Can People Use Your Device? How To Implement A Compliant Human Factors Process

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The usability of inhalation devices impacts both the ability of the patient to safely and effectively deliver therapy and the approvability of the product. Usability in device development is addressed by the discipline known as human factors engineering (human factors). To support approval of an inhalation device, manufacturers are required to demonstrate that the product user interface maximizes the likelihood that the product will be safely and effectively used by intended users, for the intended uses in the intended use environments. It is critical that human factors are considered early in the development of inhalation devices. In the US, the regulatory basis of human factors requirements is based on Medical Device Quality system regulation and is required for drug-device combination products as defined under 21CFR part 4. Several regulatory requirements are relevant, but the most applicable is the requirement for Design Validation (21CFR820.30(g)), which is also similarly specified in the EMA recognized standard ISO13485:2016 (Medical devices — Quality management systems). Design Validation requires that manufacturers validate that the device conforms to defined user needs and intended uses. In the EU, the recent advent of Medical Device Regulation (MDR, (Regulation 2017/745) also includes an increased focus on design considerations for the non-professional (lay) user. Additionally, normative human factors standards are recognized by both the EMA and FDA, and include IEC62366-1 - Application of usability engineering to medical devices, and ISO14971:2012 - Application of risk management to medical devices.

Approaches described within guidance and standards require that manufacturers follow a process to understand the user and their needs, define user centered design requirements, evaluate the user interface during development through formative evaluation and systematically analyze and manage use related risk. Formative evaluation is the process of assessing a user interface to identify the interface’s strengths and weaknesses and to identify potential use errors. Development through formative evaluation helps to identify use related risks and mitigate deficiencies in the user interface. Finally, manufacturers are required perform the summative evaluation (human factors validation) on the product user interface. Summative evaluation is conducted at the end of the user interface development process, with the final product, to obtain objective evidence that the user interface can be used safely as intended, and is often submitted in support of a device/drug-device combination product filing.
In-Vitro Measurements Of Tiotropium Aerosol Delivery From A Soft Mist Inhaler During Mechanical Ventilation

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Aerosols emitted from Respimat® Soft MistTM Inhaler (SMI) was characterized as propellant free, lower-velocity and longer-lasting than those from pMDI; however, the optimization of SMI on drug delivery efficiency in mechanical ventilator circuit has not been reported. This study was aimed to compare the efficiency of SMI to deliver tiotropium in various conditions of a mechanical ventilator through an in vitro model. The adult model was ventilated through a 7.0 mm inner diameter endotracheal tube and a filter during controlled mechanical ventilation (minute ventilation: 7.5 L/min, breathing frequency: 15 breaths/min, peak inspiratory flow: 60 L/min, ramp flow, Ti: 0.9 sec; PEEP: 5 cmH₂O). The leakage of SMI was fully sealed, and the SMI was attached to the ventilator circuit with T-piece adaptor. The major operating parameters included the timing of actuation (the beginning of inspiration, the beginning of expiration and the late period of expiration), placement of inhaler (1. between ETT and wye-piece; 2. the inspiratory limb 15 cm from wye-piece; 3. 15 cm from the ventilator), separately with dry and heated/humidified ventilator circuit (n=3). Particle size distributions in ventilator circuit were measured with an optical aerosol spectrometer (Fidas®Frog, Karlsruhe, Germany). Eluted drug from filters was analyzed by spectrophotometry (237 nm). Statistical analysis was performed with a significant level of p < .05. The amount of tiotropium delivered from SMI was greater at position 2 than position 3, regardless of whether the ventilator circuit was dry or heated/humidified (22.9%, 5.4%, p=0.04 dry condition; 13.4 %, 4.8%, p=0.04 heated/humidified). Inhaled dose was reduced by up to 42% in heated/humidified ventilator circuit compared to the dry and unheated condition. Moreover, the inhaled dose of SMI actuated at the beginning of inspiration (9.8%) and at the beginning of expiration (16.1%) was lower than that actuated at the late period of expiration (22.9%, p=0.02) under dry condition and position 2. It may result from the spray duration of SMI was longer than inspiration time. The volume median diameter (VMD) and geometric standard deviation (GSD) of aerosol emitted at position 2 and actuated at the late period of expiration were 0.8 µm and 1.56. We concluded that the optimal drug delivery efficiency of SMI counts on the inhaler position, the ventilator circuit and the timing of actuation during mechanical ventilation.
Smart Inhalers – Device And Design Technology

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Recent advances in inhaler technology have prompted the emergence of smart inhalers, enabling users and prescribers of asthma and COPD medicines to more effectively monitor the patient operation of the MDI and to track compliance and adherence in real time, including remotely. Several externally mounted smart inhalers have already received regulatory approval and are being used in clinical trials. Available technology has made it possible to incorporate a wide array of sensors into this new generation of inhalers to promote and confirm correct usage and to securely collect and transmit in-use patient data. For the past five years, H&T Presspart has been working to develop an affordable smart inhaler for global uptake. The newly launched eMDI, is a fully embedded, disposable device, designed for intuitive and discrete patient operation. The optimized design includes both electronic sensors and mechanical components to ensure essential, unadulterated, and secure data capture and exchange, at the lowest possible cost. The partnership with CoheroHealth allows seamless integration into their app and cloud based platforms to enable tracking of both control and rescue medications. In addition, real time lung function measurements can be incorporated via an approved, clinical grade, portable spirometer. The leading pharmaceutical companies have taken notice and are forging alliances to access these new devices in patient studies and clinical trials. To date, a number of clinical studies using smart devices have demonstrated significant improvements in medication adherence, less dependency on rescue medications and a reduction in emergency room visits and hospital stays. These improvements could someday directly translate to significant savings in global healthcare cost. However, the adoption of smart inhalers faces numerous challenges, from a wide range of stakeholders, including patients, prescribers, regulators, pharma, payers, and employers.

The additional cost of the smart inhalers and “who pays” is an unanswered question. As the costs of medicines, payment and reimbursement schemes differ from country to country, success will require identification of stakeholder driving forces and demonstration of added value to promote uptake. Device complexity, including feature considerations, data security, and standardized information exchange platforms will also require deliberation. In the end, smart inhalers represent new opportunities for improving the quality of life of asthma and COPD patients. The key to successful global adoption is an affordable, intuitive device, with a carefully chosen feature set, to address concerns of and drive benefits for the multiple stakeholders.
Back To The Future: Inhaled Liposomes

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The idea of delivering tiny phospholipid vehicle – liposomes - to the lung originated from Alex Bangham in 1960s who was interested in the noble pursuit of rescuing prematurely born babies with the Infant Respiratory Syndrome (IRDS). The idea of treating respiratory diseases with inhaled drugs is intuitively obvious: delivering the therapeutic agent to the site of action in high concentrations while minimizing the potential for systemic side-effects. Marrying the two concepts – liposomes and pulmonary drug delivery – became a popular research topic in the 1970s, with the view that the liposomes whose composition and membrane structure resemble human cells would act as "Trojan horses" delivering the drugs without irritating the sensitive lung surfaces and provide slow release at the site of action for persistent therapeutic effects. Yet, almost 50 years later, there are no approved inhaled liposomal therapeutics. Several factors likely contributed to this slow pace: 1) Inability to formulate liposomes with adequate storage stability and robustness during aerosolization; 2) Mismatch between the rates of release from the liposomes and absorption from the lung; 3) Wrong drug choice; 4) Misleading conclusions from inappropriate animal models; and 5) Lack of champions! The most advanced candidate products that are in, or have completed, Phase 3 clinical trials, are: a) liposomally encapsulated ciprofloxacin (Linhaliq, Aradigm Corp.) for the treatment of bronchiectasis patients chronically infected with *Pseudomonas aeruginosa*, and b) liposomal amikacin (Arikayce, Insmed Corp.) for the treatment of patients with pulmonary infections with *Mycobacterium avium*. The key lessons learned from these advanced developments should assist the future development of inhaled liposomal drugs and inhaled products in general.
The Role Of The National Chemical Laboratory In The Quality Control Of Inhalation Preparations

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The National Institutes for Food and Drug Control (NIFDC) is the only subordinate agency with quality control laboratories of the State Food and Drug Administration (SFDA). The main professional areas of NIFDC cover pharmaceutical products, biological products, medical devices, food, health food, cosmetics, reference standards, laboratory animals, and drug safety evaluation.

NIFDC owns the comprehensive laboratory for orally inhaled products (OIPs). A large number of studies have been carried out on the quality control of OIPs, mainly metered dose inhalers (MDIs), dry powder inhalers (DPIs), and inhaled solutions. The research focused on product performance, especially aerodynamic particle size distribution (APSD) and delivered dose uniformity (DDU). Chinese Pharmacopoeia adopts three apparatuses for APSD measurement, namely, the glass impinger, Aderson cascade impactor, and Next Generation Impactor. Method development and validation of APSD and DDU have been completed, such as stage mensuration, re-entrainment, and mass balance. The spray pattern and plume geometry for MDIs, interactions between API and excipients for DPIs, selection of formulation for inhaled solutions are in progress. In vitro–in vivo correlation is a challenge. NGI with an Alberta idealized throat and a breath simulator may mimic in vivo breath profiles. The establishment of dissolution tests for evaluating drug absorption in the lungs is in progress.

The appendix and the specifications of monographs of OIPs in Chinese pharmacopeia have been drawn up based on above-mentioned work. A series of articles for inhaler had been published in a column of Chinese Core Journal of Superior Quality. Some famous technical books about inhalers had been translate and published. The research group undertakes specification evaluation and review of imported OIPs, and carries out the post market surveillance testing for OIPs. The recommendations or guidelines for bioequivalence approaches of OIPs have been in consideration.
Efficient Data Analysis (EDA) vs. Fine Particle Dose (FPD)

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Aerodynamic particle size distribution (APSD), a critical quality attribute of pharmaceutical aerosols, is typically measured by cascade impaction (CI) and often accounts for > 25% of the analytical labor on an orally inhaled product (OIP). The lack of a suitable surrogate for inertial impaction techniques such as CI continues to fuel interest in the development of abbreviated impactor measurement (AIM) systems. As a complement to full-resolution CI, the AIM strategy relies on reducing the number of components in the impactor to achieve significant gains in time, labor, and solvent consumption. A variety of AIM apparatuses have emerged in recent years, most consisting of a single size-fractionating component for determination of mass below a given cut-off diameter. As these systems have inherently yielded less data than conventional CI, new approaches to data analysis and interpretation have emerged in concert with the new apparatuses. This presentation focuses on one such data analysis strategy developed by the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). This approach, termed Efficient Data Analysis (EDA), uses a combination of a large/small mass ratio and the impactor-sized mass (ISM) to detect changes in aerosol APSDs. This presentation compares the performance of EDA to that of Fine Particle Dose (FPD), the APSD quality control metric currently favored by European regulators. The comparison is based on analysis of APSD data from four products: two pressurized metered dose inhalers (MDIs) and two dry powder inhalers (DPIs). For each product, out-of-trend (i.e., atypical) APSDs are evaluated with EDA metrics and FPD. In each case, the EDA metrics easily distinguish the atypical APSDs whereas FPD does not. While FPD is capable of detecting changes in the total mass delivered to the impactor, it is relatively insensitive to changes in the central tendency of the APSD. The two EDA metrics, on the other hand, combine to readily detect changes in either the total mass or the central tendency of the distribution. EDA is thus shown to be superior to FPD for routine control of OIP quality. These results augment prior work by the IPAC-RS CI working group demonstrating superiority of EDA relative to the impactor stage grouping metrics currently favored by US regulators.
In Vitro and Ex Vivo Models to Study Inhalation Biopharmaceutics - Are We There Yet?

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The aim of this paper is to provide an update on available in vitro and ex vivo models of the lungs used as screening tools in pre-clinical inhalation biopharmaceutics. Cell culture models are a relatively quick and simple means to study mechanisms of drug disposition at the molecular level. In vitro models, however, have obvious limitations regarding, for example, their lack of clearance mechanisms or reduction to mostly a singular cell type. Some of the widely used cancer-derived cell lines, i.e. Calu-3, A549, NCI-H441 and NCI-H292 have significant shortcomings. Similarly, the first generation of simian virus (SV)40 large T antigen-immortalised cell lines (e.g. 16HBE14o- and BEAS-2B) often present phenotypes different from those of the original cell type. Novel immortalised cell lines such as NuLi-1, UNCN1-3T, VA10, BCI-NS1.1 and hAELVi appear to better resemble the native cells, but most of them have not yet been sufficiently characterised in biopharmaceutical applications.

Precision-cut lung slices can be used for lung retention and effect duration studies of inhaled drugs by measuring the unbound drug volume of distribution. Isolated perfused lungs (IPL) also offer opportunities to investigate pulmonary drug disposition. In this technique, the lungs are isolated from the systemic circulation, perfused via the pulmonary circulation and ventilated via the trachea. Using isolated perfused lungs, it is possible to deliver precise concentrations of drugs, measure bi-directional drug transfer (i.e. from lung to perfusate and perfusate to lung) and use transport pathways inhibitors in concentrations and combinations that are not possible in vivo. The effectiveness of a variety of absorption-modifying drug delivery strategies on absorptive clearance from the lungs has been investigated in IPL, including polymeric microparticles, liposomes, sequence-specific phage display-derived peptide-conjugated dendrimers, and drug-ester polymer conjugates.

The advantages and limitations of the different in vitro and ex vivo systems in which lung disposition can be studied need to be considered. Complementary study designs can be applied using triangulation to confirm hypotheses and observations. Cell cultures provide convenient systems that allow mechanistic studies. Lung slices and ex vivo lungs enable drug transport and accumulation to be studied in more complex settings. The specific information obtained from in vitro and ex vivo models can be integrated with other measured drug or formulation properties through physiologically-based pharmacokinetic (PBPK) modelling by which the complex interplay between drug properties and lung physiology can be explored and understood.
What Are The Challenges And Opportunities For Inhalation Products And The Asthma And COPD Market In China?

Anny Shen

IDDA – China

China has 27 provinces and four municipalities with a total population of 1.3 billion. The population increase in Chinese cities, large number of smokers, use of motor cars, rapid industrial expansion, and environmental pollution are major causes of human respiratory diseases. There were over 32 million asthma patients in 2016 and the incidence of asthma has been increasing at 4% per year. Among children below 14 years old, 3.7% suffer from asthma. Incidence of COPD is very high in China, with > 80 million patients in 2016. COPD sufferers comprise 8% and 15% of people over 28 years old and those over 40 years old, respectively. Due to the continuous increase in asthma and COPD, there has been an average growth of > 20% in drug treatment for the past five years. The total inhaled drug market in China was approximately 1.6 billion USD in 2015. GlaxoSmithKline, Astra Zeneca, Boehringer Ingelheim and other international pharmaceutical companies occupy 90% of the market. Increasingly more local pharmaceutical companies are getting involved in this area. In 2016, CFDA issued a new regulation requiring a linked filing registration for drug packaging, excipients, and drug products, which will pose a major challenge for local Chinese companies.