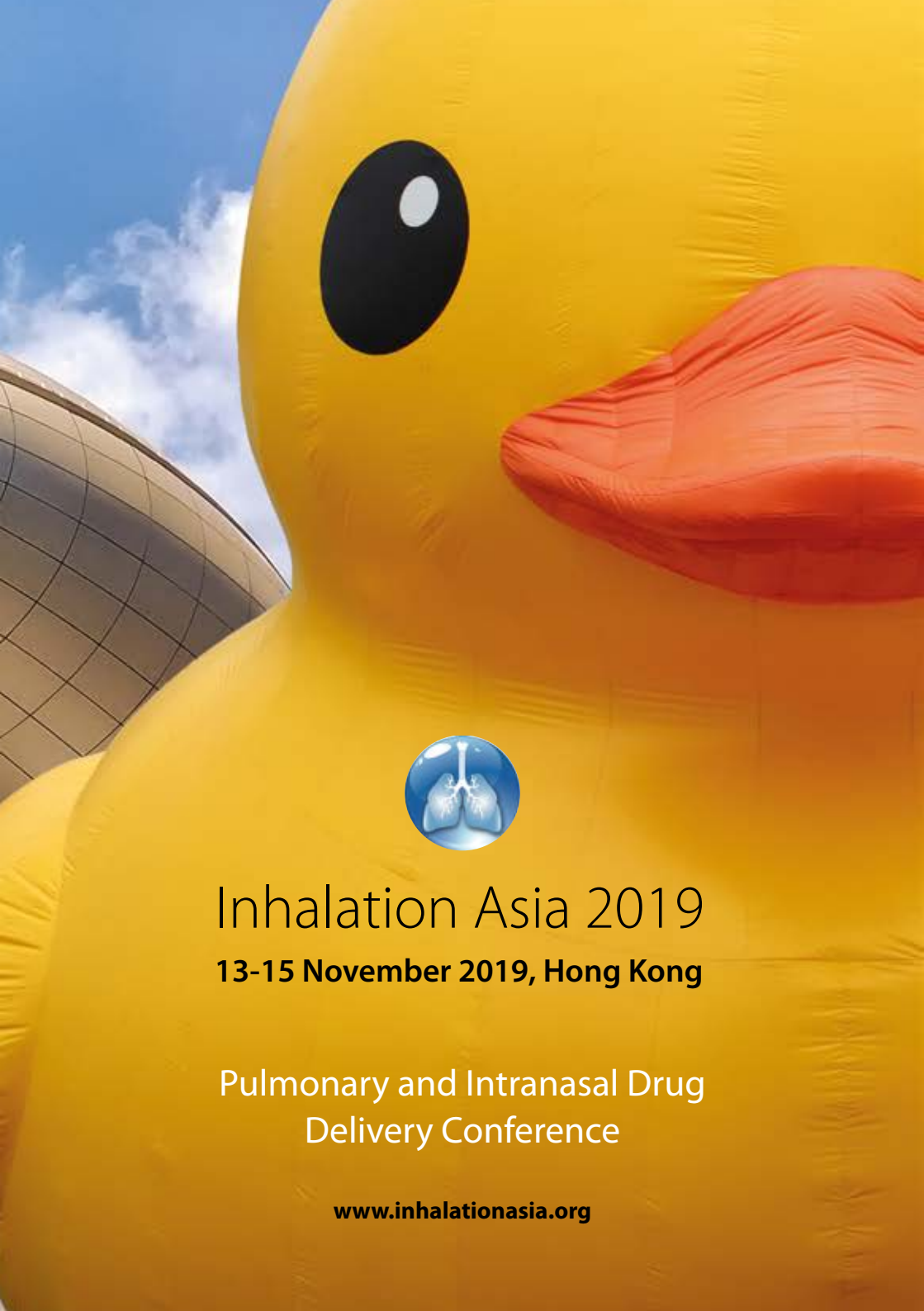

Inhalation Asia 2019

13-15 November 2019, Hong Kong

Pulmonary and Intranasal Drug Delivery Conference

www.inhalationasia.org

Foreword

Welcome to Inhalation Asia 2019

On behalf of Inhalation Asia and the Chinese University of Hong Kong, it is with great pleasure that we welcome you to The Hong Kong Science and Technology Park for Inhalation Asia 2019. We are proud to be celebrating the 8th anniversary of Inhalation Asia and the 4th edition of our bi-annual conference. Inhalation Asia has fulfilled our ambition to connect scientists and technologists working on inhalation drug delivery in the Asia-Pacific region: where East meets West.

IA19 is hosted in partnership with the Chinese University of Hong Kong.

The mission of the CUHK is to increase access to safe and cost-effective medicine. For more than two decades, the academic staff at CUHK has lived up to the tradition of bringing out the best in each student with a high quality, rigorous and dynamic curriculum. It has created a nurturing environment that cherishes teamwork, leadership and commitment to civic responsibility. The School also takes pride in being able to raise the awareness of the public in the value of those services only the pharmacists are qualified to provide. Nearly 800 pharmacists in Hong Kong are CUHK graduates, accounting for about 25% of the pharmacist work force.

The inhalation drug delivery community in Asia is growing in numbers. New companies dedicating themselves to innovation in inhalation drug delivery start every month, and a number of academic centres are now well established in the region: Hong Kong, GuangZhou, Shanghai, Shizuoka, Kyoto, Saudi Arabia, Mumbai, Vishakhapatnam, Sydney, Melbourne and Taipei.

To our great pleasure, many of the world top scientists in inhalation drug delivery have agreed to present their recent research achievements and share their cutting-edge views. The 3 days program of IA19 is packed: you will be able to attend lectures to keep up with latest news from labs around the world, discuss early phase work during the poster sessions, learn or refresh your knowledge of inhalation drug delivery during the workshops on Thursday, network during the breaks, and of course meet your suppliers and clients at the exhibition. Throughout the event you will be able to meet the suppliers you use or will be using and listen to their advice.

The program of IA19 has been tailored to capture the particularity of the Asia-Pacific inhalation world. Its focus and dynamics are different in some ways from the EU or US markets, yet call upon similar knowledge and technologies to achieve similar aims: improved therapies via inhaled drug delivery. We have brought together this uniqueness in 6 sessions that address the contemporary needs of product developers and academics. We are very excited about the discussions that will take place around developments on soft mist technologies and making generic DPIs. We are able for the first time to have a full session dedicated to OINDPs in Japan. There is much good work done in the Japanese industries and academic centres and we are pleased to be the first international conference with a full session on Japan.

Inhalation Asia is an open community of scientists and practitioners, it is a unique opportunity for all of us to meet in person, network with each other and showcase our ideas, research, products and materials.

Inhalation Asia lives beyond the 3 days event every 2 years. You can follow us on our website, on LinkedIn, on Twitter and on WeChat. Thanks to all of your efforts, support and creativity, we have been able to federate a lively online community, making Inhalation Asia more active every year.

Inhalation Asia is committed to open access to the conference materials, abstracts, lectures and posters. All practitioners in the field of inhalation drug delivery can access the conference materials as long as they are registered users on the IA website (www.inhalationasia.org).

IA19 would not be possible without the generous support or our sponsors and exhibitors. In particular, we are most grateful to our Gold sponsors: Nanopharm, Harro Hofliger, Intertek, Pamasol, Koura Global, Gerresheimer and Oxford Lasers.

In order to keep up with announcements during the conference, please make sure to join the Inhalation Asia group on WeChat. This will be the only way to know what is happening when.

We hope you will enjoy your time at IA19 and in ShaTin.

Dr. Philippe Rogueda, Dr. Anny Shen, Prof. Joan Zuo
On behalf of Inhalation Asia & the Chinese University of Hong Kong

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Programme

Wednesday 13th November 2019

11:30-13:00 **Registration, Lunch & Exhibition**

Welcome to IA19

Plenary Lecture 1

Chair: Prof. Joan Zuo, The Chinese University of Hong Kong, Hong Kong

13:00-14:00 COPD in China: burden and strategies to improve clinical management
Prof. Rongchang Chen
Guangzhou Institute of Respiratory Disease, China

Session 1 – Inhaled therapies beyond COPD and Asthma

This session is sponsored by Lindal Group

Chair: Dr. Shuguang Hou, Sichuan Purity, China

14:00-14:30 Liposomal iloprost formulation prolongs pulmonary arterial pressure reduction
Ms. Cathy Ko Chieh Chen
Pharmosa Biopharm Inc., Taiwan

14:30-15:00 An inhaled therapy for urge urinary incontinence
Dr. Qun Shao
CrystecPharma, UK

15:00-15:30 Inhaled phage therapy for MDR bacterial lung infections
Dr. Shui Yee Leung
The Chinese University of Hong Kong, Hong Kong

15:30-16:00 Tea Break

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Session 2 – Window on China

This session is sponsored by H&T Presspart

Chair: Dr. Hui Xin Ong, The University of Sydney, Australia

16:00-16:30 RNA therapeutics – how to make it inhalable?
Prof. Jenny Lam
The University of Hong Kong, Hong Kong

16:30-17:00 Intranasal delivery targeting polyglutamine diseases
Prof. Joan Zuo
The Chinese University of Hong Kong, Hong Kong

17:00-17:30 Bioanalytical challenges for inhalation drug BE studies
Dr. Min Meng
Chongqing Denali Medpharma Co., Ltd, China

17:30-18:00 Evaluation of an inhaled medicine for pulmonary fibrosis
Dr. Wen Tan
Guandong University of Technology, China

18:30-20:30 IA19 delegates cocktail reception

Presspart is delighted to invite IA19 delegates
to an evening cocktail reception and networking event
on Wednesday 13th November
at the Hyatt Regency Hotel in ShaTin.
To reserve your place and confirm your attendance,
please email emily.brett@presspart.com.

We look forward to seeing you on the night.

Harro Höfliger

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Thursday 14th November 2019

Plenary Lecture 2

Chair: Prof. Tetsuya Ozeki, Pharmaceutical Sciences Nagoya City University, Japan

08:00-09:00 Inhalation products: how much inspiration vs perspiration?
Prof. Igor Gonda
Respidex, USA

Session 3 – Developing Inhalers

Dr. Anny Shen, IDDA, China
Dr. Zhenyu Wang, Sichuan Purity, China
Dr. David Cipolla, Insmed, USA

09:00-10:00 How to please the FDA: velocity measurement in support of In-Vitro studies
Dr. Seamus Murphy
Oxford Lasers, UK

10:00-10:30 Coffee Break

10:30-11:30 Machine options for different pMDI formulations
Mr. Benjamin Margot
Pamasol Willi Mäder AG, Switzerland

11:30-12:30 Right first time: shortcuts from lab to production of inhalers.
Mr. Marco Laackman
Harro Höfliger, Germany

12:30-13:30 Lunch & Exhibition

13:30-14:30 Advanced analytical techniques for generic OIND development
Mr. Mark Parry
Intertek Melbourn, UK

14:30-15:30 New Frontiers in approval of generic OINDPs in the United States
Dr. Jag Shur
Nanopharm, UK

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15:30-16:00 Tea Break

16:00-17:00 The challenges of taking a DPI from idea to manufacturing
Dr. Wenzel Novak
Gerresheimer, Germany

17:00-18:00 MDI technology: problems, solutions and tomorrow's innovations
Dr. Tim Noakes
Koura Global, UK

Friday 15th November 2019

Plenary Lecture 3

Chair: Dr. David Cipolla, Insmed, USA

08:00-09:00 Inhalable formulation to overcome biopharmaceutical limitations
Prof. Satomi Onoue
University of Shizuoka, Japan

Session 4 – Window on Japan

Chair: Dr. Philip Kwok, The University of Sydney, Australia

09:00-09:30 Spray-freeze-dried powders for inhaled gene therapy
Prof. Tomoyuki Okuda
Meijo University, Japan

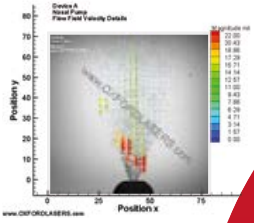
09:30-10:00 Regulatory perspective on evaluation methods for inhalations in Japan
Dr. Hiroyuki Yoshida
National Institute of Health Sciences, Japan

10:00-10:30 Coffee Break

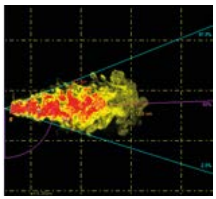
EnVision Technology

Oxford Lasers EnVision Pharma Systems.

Optical spray characterisation solution for device development and quality control.



Soft mist
Nasal
pMDI
BAI
DPI



Captures information on spray pattern and plume geometry to fulfil regulatory requirement for a range of device types

Contact: Dr. Séamus D Murphy
Imaging Division Manager

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10:30-11:00 Inkjet technology providing for uniform-sized particles
Dr. Tatsuru Moritani
Ricoh Company Ltd, Japan

11:00-11:30 Development of inhalable nanoparticles using flash nanoprecipitation
Prof. Hideyuki Sato
University of Shizuoka, Japan

11:30-12:30 Posters Pitch Session. 5 poster authors will be selected to present their work for the IA19 delegates to review and discuss.
Chair: Paul Young, The University of Sydney, Australia

12:30-13:30 Lunch & Exhibition

Session 5 – Making Soft Mist Inhalers

This session is sponsored by Proveris Scientific

Chair: Prof. Daniela Traini, The University of Sydney, Australia

13:30-14:00 Aerosol dynamics: Let's max-up the dose of the Respimat
Dr. Allen Haddrell
University of Bristol, UK

14:00-14:30 Critical Quality Attributes comparison between soft mist and pMDIs
Dr. Linda Liao
Proveris Scientific, USA

14:30-15:00 The Respimat (SMI): aerosol generation redefined
Dr. Herbert Wachtel
Boehringer Ingelheim Pharma, Germany

15:00-15:30 Tea Break

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Session 6 – Making Gx Ellipta: lessons learnt from Diskus

This session is sponsored by DFE Pharma

Chair: Dr Murray Ducharme, Learn & Confirm, Canada

15:30-16:00 Impact of solid state on inhaled particle dissolution
Dr. Fabio Sonvico
University of Parma, Italy

16:00-16:30 How to make a DPI: preparing for Ellipta
Prof. Rob Price
University of Bath, UK

16:30-17:00 In vivo bioequivalence studies for generic DPIs
Dr. Keith Gallicano
Novum Pharmaceutical Research Services, USA

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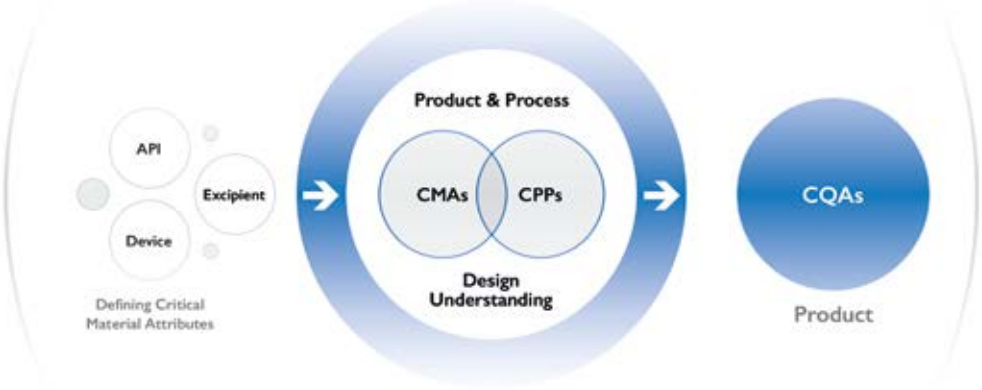

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For the Hong Kong Science and Technology Park stop University

Lecture abstracts

COPD in China: burden and strategies to improve clinical management

RongChang Chen

Guangzhou Institute of Respiratory Health, China

The characteristics of COPD cohorts exhibit significant heterogeneity, with one cohort of COPD patients in the community characterized by minimal symptoms or even no symptoms, whose underdiagnosis and undertreatment result from a low awareness of the disease, and another cohort characterized by more symptoms and frequent acute exacerbations. This cohort requires frequent medical care, consumes the majority of the medical resources, and is also associated with high mortality.

At present, inappropriate diagnosis and management of COPD are prevalent in China. A survey by Zhou Y et al. revealed that only 2.4% of the 9344 COPD patients diagnosed in a rural area had undergone pulmonary function tests. Another survey performed in 16 secondary and tertiary hospitals in Guangdong province in 2018 showed that only 14.3% of COPD patients were diagnosed on the basis of the post-bronchodilator pulmonary function. Follow-up testing of pulmonary function after one year was less than 1%.

Maintenance medication is also underused in stable COPD in China. According to the survey of 16 secondary and tertiary hospitals in Guangdong province in 2008, only 37.26% of the patients in this group received any inhaled maintenance medication after hospitalization, most commonly a LABA/ICS.

Chinese scholars have conducted a series of studies on COPD and contributed to the better understanding of progress in risk factors, pathogenesis, early diagnosis and treatment, treatment in stable COPD, immunoregulation therapy, assessment and management of acute exacerbation, as well as comprehensive management. In order to promote inhalation therapy, Chinese pulmonary experts have published a consensus on nebulization therapy and the clinical application of inhaled devices for stable chronic airway diseases. Inhalation therapy has been promoted through serial training courses and post-graduated education and a pilot project encouraging cooperation between doctors and pharmacologists seems to have increased the standardized application of inhalation therapy.

In order to further promote the improvement of COPD diagnosis and research, many pulmonary experts have actively communicated with the government to promote the inclusion of COPD as one of the key chronic diseases into the national chronic disease monitoring system in the upcoming 15 years. Correspondingly, the Ministry of Science and Technology has provided great support for the study of COPD and set up special key projects related to COPD in the area of precision medicine and major chronic diseases.

Chronic airway diseases, including COPD and asthma, were also included in the Healthy China Action 2030 action plan. The implementation and launch of this series of policies will effectively promote the progress of COPD diagnosis and treatment as well as its research in China.

Inhalation products: how much inspiration vs. perspiration?

Igor Gonda
Respidex, USA

Inhalation products need to be "inspirational" to be the preferred therapy choices. While the advantages of drug inhalation for the prevention and treatment of respiratory diseases is intuitively obvious to aerosol scientists for its high local concentrations and reduced systemic exposure, it is not the preferred route for patients or care-givers; oral therapy remains the top choice.

For crisis management, such as dealing with acute infectious exacerbations, intravenous therapy is often the first choice as it affords confident instantaneous "100% bioavailability" with few potential failure causes. For an inhalation product to be preferred over other choices, it will need to have "inspirational appeal," meaning: 1) meaningful advantages in tolerability, safety, and efficacy 2) price reflecting value 3) ease and convenience of use.

The last point has been a significant problem both for patients and product developers. Most inhalers are difficult to use, especially for patients on multiple inhaled therapies with different types of inhalers. Rates of compliance with correct technique have been low and stagnant for decades and therefore offer a great opportunity for future development of much improved technologies. Also, when the inhalation route is used for systemic drug delivery, and the high concentration in the lung is a safety problem rather than a therapeutic advantage, competitive pressures are amplified where multiple options exist.

For developers, it is important to keep in mind that patients are your most important stakeholders, and early engagement of the target population of patients in the process is essential to development of an "inspirational" therapy and to justify the development and societal costs. Direct interactions with the patient community are also supremely motivating for the product developers.

Time is a precious non-renewable resource. The practice of medicine changes rapidly, and competition to generate valuable products is likely. Executing a development plan with a significant overlap between different stages provides significant competitive advantages and is economically attractive provided that there are clear "go/go go" criteria in place. Consider, for example, running long term preclinical toxicity studies in parallel with early human studies; engaging with regulatory authorities to agree on quality control methods early on as some of these may take a long time to develop; and conducting early human factor studies to ascertain good technical compliance throughout product development.

It takes great people to make great drugs into great products. While the nature of the therapeutic agent is clearly very important, many good drugs fail during development due to teams that lacked the expertise, passion and perseverance to drive the products to approval despite all of the obstacles that inevitably arise during pharmaceutical development. The number of days when new major problems appear vastly exceeds the number of days with pleasant surprises!

Remember that science is the brain of product development but it's your heart that drives it. Research hypotheses and testing are the essence of therapeutic development, inclusive of regulatory strategy; but the passion to find a cure despite all uncertainties and obstacles is the driver of success.

IA19PL3

Inhalable formulation to overcome biopharmaceutical limitations

Satomi Onoue
University of Shizuoka, Japan

Vasoactive intestinal peptide (VIP) acts as a major peptide transmitter in the central and peripheral nervous systems and is thought to be a promising drug candidate for airway inflammatory diseases such as asthma and chronic obstructive pulmonary disease (COPD). However, the clinical application of VIP has been limited because of (1) rapid metabolic degradation and (2) systemic side effects following systemic administration.

To overcome these shortcomings, numerous structure-activity relationships (SAR) studies and pharmacological experiments have been employed in attempts to develop new VIP analogues and drug delivery systems. In our SAR studies, we successfully produced new VIP derivatives with improved metabolic stability and long-lasting effects. In addition, we developed a respirable powder formulation of VIP derivatives to maximize pharmacological effects in the airway system and to minimize systemic exposure, possibly leading to prevention of systemic side effects.

We undertook further formulation studies to develop respirable sustained-release powder formulations of VIP derivatives using a biodegradable polymer with the aim of improving the duration of action. In a rat model of airway inflammation, intratracheal administration of these new formulations resulted in marked attenuation of antigen-evoked inflammatory symptoms and neutrophilia in the respiratory system. We also synthesized a PEGylated VIP derivative by site-specific PEG conjugation at the C-terminus of a VIP derivative to further improve therapeutic potential. Conjugation of a VIP derivative with PEG produced marked improvements in metabolic stability relative to the parent peptide. A respirable powder formulation of the PEGylated derivative exhibited high dispersibility and inhalation performance, and the formulation attenuated antigen-evoked inflammatory events in a rat model of acute airway inflammation. Thus, combined use of potent VIP analogues and a targeted delivery system might provide efficacious medication for clinical treatment of airway inflammatory diseases.

IA19L1.1

Liposomal iloprost formulation prolongs pulmonary arterial pressure reduction

Cathy Ko Chieh Chen
Pharmosa Biopharm Inc., Taiwan

Iloprost is a prostacyclin (PGI2) analog approved for the treatment of pulmonary arterial hypertension (PAH). Few upper respiratory tract side effects are known for Inhaled prostacyclin therapy. In addition, iloprost has a short plasma half-life of 20-30 mins and requires frequent dosing (6 to 9 times daily) and multiple breaths/dose (total 3-8 mins) as found with Ventavis®.

A liposome inhalation formulation has been developed by PHARMOSA to provide sustained plasma concentration, which is expected to prolong pharmacological effect, as compared with current immediate-release formulation.

Liposomal iloprost formulations were prepared and characterized in terms of assay and encapsulation efficiency. The test articles were administered by microsprayer for pharmacokinetic (PK) study in rats and pharmacodynamic (PD) study in hypoxia-induced pulmonary hypertension rats. Blood samples over 12 hours post-dosing were taken and analyzed by LC-MS-MS. Pulmonary arterial pressure and systemic arterial pressure were recorded by implanted probe through the PD experiment.

Liposomal iloprost formulation showed the detectable plasma level over 12 hours in rats, as compared to iloprost solution which disappeared in one hour. High drug encapsulation reduces the dumping phenomena. In the iloprost solution group, pulmonary arterial pressures (PAP) were reduced, and then rapidly returned to the baseline. In addition, it was noted a considerable reduced systemic arterial pressure in 5 minutes post-dosing. In liposomal Iloprost group, the reduction of pulmonary arterial pressure lasted for 8 hours. There was no obvious reduction in terms of systemic arterial pressure.

Liposomal iloprost inhalation formulation demonstrates an extended plasma level and sustained pharmacological effects. It shows the potential of inhaled liposomal prostacyclin therapy with appropriate delivery device.

An inhaled therapy for urge urinary incontinence

Qun Shao
CrystecPharma, UK

Urge Urinary Incontinence (UUI) affects 200m people worldwide and greatly impacts their quality of life. Current oral medications for UUI are associated with substantial side effects (e.g. dry mouth, constipation), and an estimated 59% of patients discontinue use within six months of starting treatment. CrystecPharma has developed CR002, a dry powder inhalation (DPI) formulation of an existing short-acting anticholinergic medicine, to offer UUI patients an alternative 'on-demand' means of managing their condition. Inhaled therapy enables rapid onset of action when needed, with a short duration to reduce the side effects associated with chronic treatment. Key to the performance of CR002 is achieving exceptionally high levels of lung deposition in order to minimise oral exposure.

We used our modified supercritical anti-solvent (mSAS®) technology, a thermodynamically stable, scalable, 'bottom-up' particle formation process, to engineer drug particles of CR002. The process involves using supercritical carbon dioxide to rapidly remove solvent from a drug solution through a novel nozzle assembly, allowing controlled and fast precipitation of dry, uniform drug particles.

Typically, mSAS® particles have a narrow size distribution and low levels of surface charge, which greatly enhances aerosolisation performance and makes it possible to achieve improved lung delivery compared with conventional particle engineering techniques, even when using simple devices. In this case, an 'off-the-shelf' capsule-based inhaler, the Plastiape RS01, was selected to simplify downstream manufacturing and reduce cost. Drug particles with an aerodynamic shape and optimised size range were generated (e.g. D90 = 3 µm). In-vitro testing performed using an Anderson Cascade Impactor (ACI) showed that a 68 % fine particle fraction (FPF) as a percentage of total emitted dose (TED) was achieved, which was much greater than achieved with a micronized alternative (26%), confirming the potential for reduced oral exposure using mSAS® particles.

In-vivo testing demonstrated that therapeutic concentrations of CR002 were quickly achieved, reaching ~ 80 % of Cmax in 10 minutes, which was the first measurable time point. Rapid clearance was also observed, with concentrations falling below therapeutic levels in under 2 hours. Plasma concentrations were dose proportional over 4 different exposures by inhalation, demonstrating the opportunity for rapid intervention upon onset of UUI symptoms as well as for the possibility of use as prophylactic treatment.

These results indicated that 'on-demand' CR002 could offer patients a therapy with fewer side effects over the course of a day compared to long-acting oral therapies. This new inhaled modality will also enable patients to actively manage their own condition, whilst reducing their overall long-term anticholinergic burden, which is associated with muscle weakness and cognitive impairment.

The high level of lung deposition achieved with mSAS® particles offers the potential for other therapeutics to be systemically delivered through the lungs with an increased emitted dose whilst minimising oral exposure in a form that enables delivery by off-the-shelf inhalers.

IA19L1.3

Inhaled phage therapy for MDR bacterial lung infections

Shui Yee Leung
The Chinese University of Hong Kong, Hong Kong

The Misuse and overuse of antibiotics have significantly increased the emergence of multidrug-resistant (MDR) bacteria, posing a high risk for global health. Bacteriophage (phage) therapy, which employs lytic phage (bacteria eaters) to kill bacteria that cause infections without harm to human cells and commensal bacteria, has recently been rediscovered as a promising alternative to conventional antibiotics.

For lung infections, direct delivery of phage to the respiratory tracts is the preferred route for optimized therapeutic outcomes. Nebulization has been the most popular approach to deliver phage for respiratory infections in early research. While reduced infectivity of phage due to the nebulization process has been reported, exact reasons attributed to the reduction were unknown. We employed transmission electron microscopy to provide the first visual evidence on the structural change of phages with different tail morphologies (Myoviridae, Siphoviridae, and Podoviridae) upon nebulization, providing important insights in the choice of delivery methods for inhaled phage therapy.

Since powder formulations are generally preferred over liquids for easy storage, transport and administration, we have first compared the performance of two dry powder formation techniques, spray freeze drying (SFD) and spray drying (SD), to produce inhalable powders of a Pseudomonas phage PEV2. The SFD using an ultrasonic nozzle resulted in a 2 log production loss, whereas the SD process only resulted in a 0.75 log loss, suggesting that SD is a more suitable technique.

In our follow up studies, we demonstrated that simple excipient systems containing trehalose and leucine were sufficient to produce stable inhalable phage powders (PEV2 and PEV40) stored under low relative humidity (< 20%) at both 4 and 20 °C. Reasonable long-term storage stability was achieved with ≤ 1 log titer loss over 12 months, and an in vitro lung dose on the order of 107 pfu was obtained throughout the storage period.

Recently, we have extended the powder production protocol to an Acinetobacter baumannii phage (vB_AbaM-IME-AB2). The production loss (< 1 log), storage stability (< 0.4 log in 3 months), and in vitro lung dose (~6×107 pfu) were all comparable to the Pseudomonas phage powders, indicating the robustness of the phage powder production method.

The potential of phage-encoded proteins in controlling bacterial infections has also gained increasing attention. Endolysins (lysins), which are hydrolases that degrade the peptidoglycan wall of infected bacteria to release progeny phages at the end of the lytic cycle, are the most studied phage-encoded proteins.

We assessed the delivery efficiency of a modal lysin (EF2) to the lungs using nebulization. Our preliminary results showed negligible activity loss of nebulized EF2, supporting the feasibility of inhaled lysin therapy. In summary, developing stable formulations of phage and phage-encoded lysins for pulmonary delivery potentially provide effective treatment options for respiratory infections caused by MDR bacteria.

IA19L2.1

RNA therapeutics – how to make it inhalable?

Jenny Lam
The University of Hong Kong, Hong Kong

Pulmonary delivery of messenger RNA (mRNA) has considerable potential as therapy or as a vaccine for a range of lung diseases. Inhaled dry powder formulation is particularly attractive as it could maximize the concentration of mRNA therapeutics in the lung for local action while minimizing systemic side effects. A safe and effective delivery vector as well as a suitable particle engineering method are required to produce a dry powder formulation that is respirable and mediates robust transfection in the lung. Here, we introduce a novel non-viral vector, synthetic KL4 peptides for mRNA delivery.

These cationic peptides could form complexes with mRNA through electrostatic interaction, and we successfully formulated them into dry powder by spray drying (SD) and spray freeze drying (SFD) techniques. Both SD and SFD powder formulations exhibited satisfactory aerosol properties for inhalation, with mass median aerodynamic diameter below 5 µm. More importantly, the biological activity of the peptides/mRNA complexes were successfully preserved after drying as demonstrated in both in vitro and in vivo transfection studies.

Both the liquid and powder aerosols of peptide/mRNA complexes achieved high luciferase expression in the deep lung region at 24 hours following intratracheal administration in mice. Overall, the KL4 peptides have considerable potential to be developed as a non-viral vector for mRNA pulmonary delivery in inhaled dry powder form for therapeutic as well as vaccine applications.

IA19L2.2

Intranasal delivery targeting polyglutamine diseases

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Polyglutamine (polyQ) diseases are a group of inherited neurodegenerative disorders (including Huntington's disease) caused by the expansion of the trinucleotide repeat CAG RNA. No effective treatment for polyQ diseases has been reported so far. In pre-clinical research, DB213 was recently identified as an inhibitor targeting CAG-repeated RNA toxicity in both in-vitro EGFP78CAG RNA expressing SK-N-MC cell model and in-vivo in a drosophila Huntington's disease model, which makes DB213 one of the most promising candidates for pathogenesis-based treatment of polyQ diseases.

With increasing evidence demonstrating that intranasal delivery of therapeutics has the potential to bypass the blood-brain barrier (BBB), our current study was designed to investigate the pharmacokinetics as well as pharmacodynamics of DB213 via intranasal delivery in various animal models. Systemic bioavailability of DB213 in SD rats via intraperitoneal, oral and intranasal route was found to be 74 %, 0 %, and 8.7 %, respectively, with the unbound brain-to-plasma ratio via intravenous, intraperitoneal, oral and intranasal to be 0.00038, 0.000051, 0, and 0.16. These results suggest that intranasal administration has the potential to increase the brain uptake of DB213.

A pharmacokinetic modeling approach was employed to quantitatively demonstrate that 65.1 % of DB213 was absorbed from the nasal cavity and transported to the brain via the nose-to-brain pathway and 7.8 % was absorbed via the nose-to-cerebrospinal fluid (CSF) pathway. Moreover, the brain distribution kinetics of DB213 via the intranasal route demonstrated that both the olfactory bulb and the trigeminal nerve served as entry points to these two pathways to the brain.

To further enhance the brain uptake of DB213, an in-situ thermosensitive gelling system was developed and optimized by a design of experiments approach. The in-situ thermosensitive gelling system of DB213 demonstrated relative bioavailability of 145 % in SD rats, 165 % in C57BL/6 (wild type) and 178 % in R6/2 Huntington's disease mice with significant increase in brain uptake compared to that of DB213 in an aqueous solution.

After treatment of R6/2 mice at 25 mg/kg over 28 days, the DB213 in-situ thermosensitive gel group showed significant improvement in exploration ability and motor function as demonstrated from open field and rota-rod tests in comparison to vehicle group. The current study demonstrated for the first time improved systemic bioavailability, brain uptake and pharmacodynamics effects for intranasally-delivered DB213 in-situ thermosensitive gel, which could serve as a potential treatment for polyQ diseases.

Bioanalytical challenges for inhalation drug BE studies

Min Meng

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Many factors affect the development of orally inhaled drug products (OIDPs). Specifically, three critical elements (drug product, clinical trial and bioanalysis) play equally important roles for a successful bioequivalence (BE) study. The Cmax (maximum plasma concentration) of most inhaled drug is typically below 100 pg/mL. Hence developing a sensitive and robust LC-MS/MS bioanalytical method is critical; and even when using state-of-the-art LC-MS/MS analytical instruments such detection levels can be extremely challenging to achieve.

Over the years, we have developed a wide range of LC-MS/MS methodologies for inhaled drugs at sub-pg level lower limit of quantification (LLOQ). This presentation discusses three case studies, elucidating strategies and critical key points of these inhaled drug LC-MS/MS methodologies. These studies evaluated simultaneous quantification of budesonide (3 pg/mL LLOQ) and formoterol (1 pg/mL); simultaneous quantification of fluticasone (1 pg/mL LLOQ) and salmeterol (1 pg/mL LLOQ); and quantification of tiotropium (0.2 pg/mL LLOQ).

Budesonide is a corticosteroid with a four fused ring structure, while formoterol is a long-acting β2 agonist, a phenylethanoloamine. The challenge was to develop a single method to simultaneously quantify both analytes with the lowest LLOQ as possible. A single solid phase extraction (SPE) with two-step elution allowed us to develop an LC-MS condition suitable for each analyte in order to maximize the sensitivity. Using a Biphenyl LC column, acidic mobile phases, and gradient elution, we found that the LLOQ for formoterol was at 1pg/mL. The LLOQ for budesonide was measured at 3 pg/mL using a C8 LC column, basic mobile phases, and gradient elution. A formal validation following bioanalysis guidance was conducted with great precision and accuracy.

The methodology for fluticasone and salmeterol was similar to the first example, because like budesonide, fluticasone is a corticosteroid and like formoterol, salmeterol is a long acting β2 agonist. One unique facet of the fluticasone method development was the selection of the ionization mode because fluticasone's ring structure has no distinguished acidic or basic functional group, so it can be ionized under either positive or negative ion modes. Although a positive ion mode yielded a 10-fold higher signal during the infusing experiment, the negative ion mode was ultimately selected based on the signal-to-noise ratio of the LLOQ extract. A formal validation was also conducted for this combined method with LLOQ at 1 pg/mL for both fluticasone and salmeterol.

The Cmax of inhaled tiotropium can be as low as 15-20 pg/mL, and this method was previously validated in our lab twice, once with a LLOQ at 1 pg/mL once at 0.5 pg/mL. The new, more sensitive method is validated with a LLOQ of 0.2 pg/mL using the most advanced mass spectrometer.

In summary, we found that bioanalytical LC-MS/MS methods for inhalation drugs often require large sample volumes, complex and orthogonal sample extraction procedures, 2- or 3-dimensional comprehensive liquid chromatography conditions, the most advanced mass spectrometer, and well thought method development to achieve the desired LLOQ.

Evaluation of an inhaled medicine for pulmonary fibrosis

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STV, A plant derived medicine, has found to be effective against pulmonary fibrosis as an inhaled aerosol formulation. In Vitro and In Vivo evaluations were performed in combine with DESI mass spectrometry imaging (MSI) and computed tomography (CT). Two nebulizers with different mechanisms were tested to compare efficacy of delivery.

In the In vitro study, the percentage of total amount of STV delivered by Pari sprint (jet nebulizer) and Omron nebulizer (vibrating-mesh nebulizer) were 86.4 % and 93.04 % respectively; the volume median diameter (VMD) were 2.76 μm and 5.52 μm respectively.

In Vivo (in a mouse model), the lung distribution of STV aerosol from both Pari sprint and Omron nebulizer were evaluated using DESI MS imaging. After inhalation for a period of 30 minutes, the left lung was taken and frozen. It was then carefully cut into three sections which anatomically represent three main portions of lung: main bronchi (inner section), bronchiolar (middle section) and alveolar (lateral section). The relative deposition of STV in each portion of the lung were scanned by Deci MS imaging. The deposition of STV at bronchiolar and alveolar regions were higher when the Pari sprint nebulizer was used in comparison to the Omron nebulizer.

Pulmonary fibrosis was induced by bleomycin (BLM) in rats. Inhalable STV aerosol was delivered into a close rat chamber using Pari sprint nebulizer. An STV aerosol formulation (4 ml at three different concentrations: low dose 1.25 mg/mL, middle dose 2.5 mg/mL, high dose 5 mg/mL) were delivered and inhaled by rats for 30 mins, twice a day, for 28 consecutive days. A saline aerosol was used in the control group. Oral Pirfenidon (100 mg/kg, twice a day) was used as the positive control group.

The fibrosis areas in both lungs were detected and quantified using a computed tomography(CT). Pulmonary functions including total lung capacity (TLC), forced vital capacity (FVC) residual volume (RV), inspiratory capacity (IC), dynamic compliance (Cdyn), static compliance (Cst) and maximum mid-expiratory flow (MMEF) were evaluated in the same animal in each group. BLM induced a large area of fibrosis in both lungs, along with a significantly reduced respiratory function.

After treatment with the STV aerosol, the fibrosis area was significantly diminished and the lung function was significantly recovered in comparison to the BLM group. The effect of the STV aerosol treatment was similar to the Pirfenidon (given orally) dosing. In a separated group, STV aerosol was given to normal rats for 28 days and no noticeable stimulating effects of STV on normal lung tissue were found in comparison to the saline group. There were significantly increases in collagen deposition (masson trichrome staining) and severe inflammatory infiltration (HE staining) in the BLM group. These pathological changes in BLM rats were significantly ameliorated after STV treatment.

In summary, inhaled STV aerosol is as effective as oral Pirfenidon in against pulmonary fibrosis. The deposition of STV in both bronchiolar and alveolar regions were higher using the Pari sprint nebulizer than with the Omron nebulizer.

IA19L3.1

How to please the FDA: velocity measurement in support of In-Vitro studies

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In May 2019, the FDA released draft guidance document on Beclomethasone Dipropionate which makes recommends for in vitro and in vivo studies to establish bioequivalence. As part of this document the FDA ask for additional supportive in Vitro studies on velocity profiles of the aerosol spray. This marks a step change in data requirement within the guidance documents and introduce additional measurement on the generics sector in establishing bioequivalence.

Scientists and device engineers have used image-based systems to capture velocity data from respiratory devices for over four decades. Employing system to capture a combination on qualitative and quantitative information to help answer question on the development and understanding of the complex transient spray generated from a respiratory device. To measure velocity profiles, a high-speed imaging system is configured to capture pairs of images with a define time separation to provide a particle shift no greater than 10 pixels. A high-speed camera operating at up to 1000 pairs of images per second and short pulsed laser are used to capture and illuminate the transient spray event. Flow field analysis software is used to determine velocity data for each pair of images through the transient event. The following presentation, sets out to show how velocity profile data can be captured for the FDA guidance requirement. The presentation presents data for both standard pMDI and BAI type respiratory device. On device actuation the global velocity data captured shows a rapid increase in particle velocity to its peak. Beyond the peak velocity, results show the velocity decreases over the remaining event duration. Studies from multiple actuations show the velocity profiles to be consistency & repeatable. Studies across device type show difference in velocity profiles, with changes in the initial release velocity intensity, the positon and scales of the peak velocity and the rate of decline in velocity beyond the peak velocity.

FDA Velocity profiles will provide regulator with understanding of the device platform performance and allow comparison between RLD and Test devices.

Machine Options for Different pMDI Formulations

Benjamin Margot
Pamasol Willi Mäder AG, Switzerland

Whether a pressurized metered dose inhalers (pMDI) formulation consists drug solid (API), solvent, and liquid propellant or API and liquid propellant only, ensuring the consistency of the drug dose content uniformity (DDCU) by controlling the net fill weight of each can and the ratio of the API, the formulation, and any propellant is critical.

A typical product concentrate fill is 1.0 g with a filling tolerance of +/- 0.05 g in accordance with the FDA requirement for the ratio of drug/propellant of +/- 5 %. Achieving this tight tolerance in a complete filling system consisting of the process vessel, mixing device, pump, and filling system is a challenge.

pMDIs may be filled in either one or two stages. For two stage filling, the API is mixed with a solvent and filled into an open can, then the propellant is filled under pressure after the valve has been placed and crimped. The most important factor affecting the DDCU for this process is the accuracy and repeatability of both the drug concentrate fill and the propellant fill. If both stages are filled and controlled accurately, the filled can will contain the correct concentration.

After the concentrate has been filled into the can, the valve is inserted and crimped to seal the valve to the can in order to contain the contents and prevent leaks for the life of the product. The crimp is controlled by measuring and setting the crimp compression force, crimp height, and crimp diameter. These parameters ensure that the neck gasket is correctly compressed, and that the compression is maintained.

The final stage of the process is the propellant fill, and to ensure that the correct volume is filled, the delivery of propellant to the filler (at 10 bar constant pressure) must be controlled and the propellant maintained at a constant and stable temperature.

For single stage filling, the API is mixed with the propellant (and solvent if required) in a mixing vessel and the resulting suspension is filled under pressure through the crimped valve into the can. The most important factor affecting the DDCU for this process is the accuracy and control of the batch manufacture in the mixing vessel system as well as the delivery of the product to the filling machine. If these processes can be carried out and controlled correctly, then we can ensure that the correct concentration is filled into each can.

Single stage formulations can be filled in two ways; by filling the suspension and removing the residue with vacuum (aspirator fill) or by filling the suspension and flushing the residue through the valve with propellant (dual fill). The aspirator filling process can be problematic because the suspension residue can block the vacuum pipework, leaving residue on the valve, can, and filling nozzle, so dual fill is a better process.

The Pamasol tandem diaphragm pump delivers a constant 10 bar supply pressure with minimal fluctuation to ensure that the suspension is homogeneous, the propellant is compressed into its liquid form, and the fill is correct. This pump is unique and has been designed specifically for this process.

Right first time: shortcuts from lab to production of inhalers.

Marco Laackman
Harro Hofliger, Germany

Several methods are available for industrial filling of different types of dry powder inhalers (DPIs), which may require filling of the powder into blisters, cartridges, discs, or capsules. The most commonly used filling technologies for DPIs are vacuum drum, dosator, membrane, and screw auger filling, each of which is related to a particular type of DPI. Factors such as electrostatic powder behaviour, dosing speed, and fill weight accuracy can make scale-up from lab to production scale filling a challenge.

Several case studies demonstrate machine design and process parameter development technical measures we have taken to improve the fill weight results in the course of scale-up activities. The importance of joint product and process development is related to physical powder characteristics like specific flow energy, compressibility, particle size distribution, and the ability to fill a given formulation in an early development stage.

Membrane filling has a limitation due to powder compressibility for large particle sizes. Screw auger systems require a higher specific flow energy with a D90 > 120 µm while the drum dosing technology is robust and accurate to handle various type of powder formulations from coarse to purely micronized. Powder properties influence the fill weight accuracy and lead to observed relative standard deviations between 1-8 % for chosen filling technologies. Such machine performance can be improved once the powder characteristics are known.
In the case of dosator filling, it is possible to switch the process from a standard dosing procedure for coarser powder to a powder pre-consolidation process in the case of higher fines content. Also, the powder bed height in dosator filling has a major influence on fill weight accuracy. In other cases, the powder metering and filling technology influences drug product performance (i.e., emitted dose or fine particle dose).

In contrast to free flowing powder, another technology utilizes cohesive powder properties to improve fill-ability. The handling of purely micronized substances takes advantage of inter-particulate forces to form particle agglomerates which improve powder feeding and metering processes.

To handle both the inhaler formulation development and up-scaling in tight project frames, developers need to define inhaler technology for a thorough assessment of critical product and powder process interactions.

IA19L3.4

Advanced analytical techniques for generic OINDP development

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In vitro bioequivalence testing for the development of successful generic inhaled pharmaceutical products continues to pose a challenge for the industry due to the need for analytical strategies that will satisfy both the continuously evolving requirements of regulators and the need for a robust development process.

New, powerful analytical strategies are necessary to allow for production of stronger in-vivo data packages that could support greater clinical success as well as the possibility of successful in-vitro only generic approvals. Several advanced techniques are available to improve the robustness of development programs with a goal of de-risking clinical studies or further bridging in vitro-in vivo correlation (IV-IVC) to strengthen in-vitro data submissions with a view to potentially avoiding clinical work altogether.

As regulators have produced general and product-specific guidance, they have advanced expectations for in-vitro testing programs, adding newer techniques such as spray pattern/plume geometry testing for MDIs and requiring a clearer focus on identifying and controlling critical quality attributes as an integral part of development. Current guidelines recommend the inclusion of flow rate studies to explore the behaviour of DPI products at higher and lower flowrates than are typically used for testing of the product. These tests do not provide effective simulation of the actual behaviour observed in either healthy or inhalation-compromised subjects, who generate a range of flow profiles.

A much more biorelevant test that can be incorporated into the aerodynamic particle size distribution (APSD) and emitted dose (ED) testing and that can provide more clinically relevant data is available and pays particular attention to the impact of the patient's condition on the typical inhalation manoeuvre.

While impaction testing provides good information on the aerodynamic size of the inhaled product, it should not be relied on to predict the likely behaviour of the drug when deposited in the lung. In addition to particle size, factors affecting dissolution and absorption of the API include particle morphology, salt and crystal form, which are all likely to have an impact. Work continues across the industry to develop and optimize lung dissolution models to allow for assessment of the dissolution behaviour of the delivered API. Key challenges include the preparation of a suitably representative sample for testing and the identification of suitable biorelevant and discriminatory test conditions.

Recent work suggests that morphologically directed Ramen spectroscopy (MDRS) can be a useful orthogonal technique to compliment impaction, allowing for the investigation of individual size fractions and the generation of information regarding particle morphology to be generated and compared. The technique also shows promise for assessment of deposition behaviour by allowing for direct measurement of information regarding the deposition and distribution of API only, API/carrier, API1/API2 and API1/API2/carrier particles, which has not previously been practical.

New Frontiers in Approval of Generic OINDPs in the United States

Jag Shur
Nanopharm, UK

- Inhaled pharmacokinetics (PK)
- Regional deposition modelling
- Dissolution
- Morphology-Directed Raman spectroscopy
- Physiologically-based PK modelling

In opening the ANDA pathway for orally inhaled and nasal drug products (OINDPs), the FDA has introduced the concept of microstructural equivalence (Q3) for local acting products that are qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug products (RLD); in terms of their active and inactive pharmaceutical materials. The microstructural differences in the arrangement of matter and state of aggregation within formulated and aerosolized forms of OINDPs will be highly dependent on physicochemical properties of active and inactive materials, device characteristics and processing history. Differences in Q3 at both a microscopic and macroscopic scale could manifest itself as a difference in properties that could be characterised using a combination of orthogonal in vitro or ex vivo based techniques. Some of the techniques currently under assessment for characterising Q3 for OINDPs include the use of morphologically directed and surface mapping Raman spectroscopy (MDRS) and an integrated measurement of structure through in vitro dissolution and permeability kinetics.

We have investigated the particle size of commercial drug substance supply of four batches of Mometasone Furoate using conventional laser diffraction and MDRS. These data suggested that batches 1 and 4 were the largest and batch 2 was the smallest in terms of particle size. Analysis of nasal suspension formulations containing these API batches were analysed by MDRS. Comparison of the laser diffraction and MDRS data suggested that the MDRS method was able to track the drug substance particle size in the nasal suspension formulation.

A combination of MDRS and dissolution analysis has been employed to investigate the microstructure of Advair Diskus. These data show the presence of "free-standing" or discrete API together with mixed agglomerates within the aerosolized dose as a percentage of the total particles analysed in each case. The percentage of discrete FP increased with increased concentration of FP in the powder blend. Moreover, the presence of FP-lactose-SX agglomerates decreased as the dose strength of FP in Advair increased. A comparison of these data with the dissolution data presented implies that the faster dissolution of FP from the US Advair Diskus 100/50 µg low dose product may be related to the smaller amount of discrete FP alongside the increased FP agglomeration with more soluble components, lactose and SX, that could accelerate FP dissolution.

The concept of Q3 structural equivalence for OINDPs has been introduced to improve both the scientific understanding of the fate of the dose delivered locally intranasally or to the respiratory tract.

The challenges of taking a DPI from idea to manufacturing

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Making DPI devices is a long and systematic process that involves multiple stakeholders: users, developers, engineers, regulators, lawyers, marketers and more. Through the journey of a capsule inhaler device from idea, industrialisation to commercial manufacturing we will highlight the process of making a device to help you plan your own projects for success.

Do not start without a firm idea of your goal. Evaluate the economics of your market, the imperatives of the manufacturing you envisage. Designing a device is easy, designing a device that can be manufactured is more difficult: perfection is the enemy of good. Thinking about the regulatory and market imperatives alongside the device design will save you time in the long run; changes at a later stage are costly. The clearer your vision for your device, the more chances you will have to stay within budget.

Your vision will shape the product specifications; turning device ideas into well-defined and balanced product specification is key. Which parameters will affect product quality, assembling stability and reduce the costs of the final product?

DPI device are high precision assemblies of "plastic" moulded and metallic parts. Making tools to mould device parts is subtle; 20 µm is small but makes a big difference to the quality of a part. Allowing enough time to test run polymers with different masterbatch qualities is important and an integral part of a project plan.

Components handling is next: for a capsule inhaler avoiding needle damage during automated handling is a must coupled with detection systems; camera inspection systems reduced the needle handling failure rate of the capsule DPI to 2%. Monitoring statistics is essential for a meaningful root cause analysis of the device manufacturing and performance.

Surface The inner surface of the product will influence the pharmaceutical capability and needs to be addressed. Nevertheless the cosmetic, the outside finish will be relevant for the success in the hands of patients too. How much are cosmetic factors relevant to a success story?

The journey of a new device includes validation and qualification steps. Timeline and cost effects must be planned and quantified. The journey of this capsule inhaler will show you how to navigate a device industrialisation.

IA19L3.7

MDI technology: Problems, solutions and tomorrow's innovations

Tim Noakes, Mark Sanders
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As more companies enter the MDI technology space, we continue to receive questions on a number of matters that continue to cause trouble, especially for newer entrants. Development of bad taste can be due to heterogeneously catalysed oxidation of ethanol in the aerosol producing acetaldehyde which can lead to loss of sales. Attention to valve storage conditions can combat this. Erratic fill weights can arise through the formation of micro-bubbles due to cavitation in pumping propellant, inclusion of gases such as nitrogen in the process makes this worse, as do restrictions in the propellant feed to the pump. This leads to manufacturing loss and compliance issues. Specialized design of the propellant feed and delivery piping can minimise this effect.

A new problem is the developing global focus on regulatory control of HFC emissions as a contribution towards reduction of man-made global warming, enforced by the Kigali Amendment of the Montréal protocol which will reduce global emissions of these gases to 15% of the current carbon equivalent amount. These regulations will come into force in Non-Article 5 countries 2020-2030, and in most Article 5 countries, including China, 2030-2040. At present there is no exemption for pMDI propellants.

Considering this, Koura has been developing HFC 152a (1,1-difuoroethane) as a low carbon alternative HFC propellant. Safety studies are advanced, with most complete and the 24 months lifetime study in the rat proceeding. Cradle to grave whole life carbon foot printing shows that the whole device carbon footprint for a 152a MDI is similar to that of a typical m-DPI. This should secure and expand the future of the pMDI dosage form for the long term.

The single largest issue facing the pMDI is probably user coordination. Koura believes that if this can be properly addressed, the pMDI's many other advantages would then make it the most attractive portable respiratory dosage form for most small molecule treatment. With that in mind Koura have invited Clement Clarke to present their latest work.

The GINA guidance recognizes inhaler technique training as important; and pMDI technique training aids exist, but the majority of those aids are used only for initial familiarisation. Clement Clarke's Clip-Tone, a novel inhaler add-on that emits an acoustic signal, can aid in developing good technique both directly and via a smartphone app that provides patient feedback and adherence monitoring. The Clip-Tone is a low cost option that can be used on a daily basis without altering the delivered dose from the pMDI and without the need for batteries.

Delivery data for pMDIs with and without Clip-Tone demonstrate consistent delivery throughout the flow rate range of Clip-Tone whistle, and patient feedback data show patients developing greater confidence. Ongoing clinical data also reveal that Clip-Tone helps patients to conform to usage instructions in a more consistent way. Early data on development of two distinct acoustic signals (for reliever and preventers), and of novel actuator bodies with built-in Clip-Tone functionality, show broad applicability.

IA19L4.1

Spray-freeze-dried powders for inhaled gene therapy

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Spray freeze drying (SFD) was used obtain highly porous dry powder particles. We have introduced this technique for the development of dry powder inhalers (DPI).

We added leucine (Leu) as a dispersion enhancer to improve the aerosol performance of SFD powders. We demonstrated the effect of Leu in SFD powders to be within the range of inspiratory flow rates achievable for human subjects in various inhalation devices with different aerosol resistances.

We produced SFD pDNA powders by applying chitosan and synthetic degradable polymers (PAsp(DET) homopolymer and PEG-PAsp(DET) block copolymer) to form nano-sized complexes in water. Agarose gel electrophoresis analysis clarified that the addition of these cationic polymers could help keep the structural integrity of pDNA.

In an in-vivo gene transfection study by intratracheal administration into mice, the SFD pDNA powder with PAsp(DET) exhibited much higher gene expressing effect in the lungs than the original solution before the SFD process .We also found that the application of hyaluronate produces SFD naked pDNA powders that showed superior gene expressing effect in the lungs.

Polyethyleneimine (PEI) and self-assembled lipid nanoparticles (SLNP) were used in the production of SFD siRNA powders. The SFD siRNA powders with PEI and SLNP had high aerosol performance similar to the powder without siRNA, and they maintained the structural integrity of the siRNA. After dissolution of these SFD powders in water, the reconstituted siRNA/PEI complexes kept the physicochemical properties and in vitro gene silencing activity of the original complexes constituted before SFD, whereas the siRNA/lipid nanoparticles were spontaneously constituted with relatively high particle size uniformity and strong in vitro gene silencing activity.

In in-vivo studies by intratracheal administration into lung metastasis mice and healthy mice, the SFD siRNA powders with PEI and SLNP showed strong and specific gene silencing effect against tumours metastasized to the lungs, and they caused no significant increase of injury markers. A biodistribution/stability study of Cy5.5-labeled siRNA demonstrated that the SFD siRNA powder with SLNP showed both more prolonged retention and higher stability of siRNA in the lung than the naked siRNA solution.

Regulatory perspective on evaluation methods for inhalations in Japan

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In the Japanese Pharmacopoeia (JP), dosage forms are classified mainly by administration routes and application sites and, as of the 16th revision in 2011, are further subdivided according to their forms, functions and characteristics. Three inhalation dosage forms -- dry powder inhalers (DPIs), inhalation liquids and solutions, and metered dose inhalers (MDIs) -- are listed as preparations for inhalation intended for administration as aerosols to the bronchial tubes or lung.

Appropriate control of delivered dose uniformity and aerodynamic particle size distribution, which are important quality characteristics of DPIs and MDIs, is required. Two general tests, "6.14 Uniformity of Delivered Dose for Inhalations" and "6.15 Aerodynamic Particle Size Measurement for Inhalations", were discussed by the Inhalation Working Group and published in Supplement 1 to JP 17th revision. In parallel, the harmonization of the two general tests in the Pharmacopeial Discussion Group (PDG) had been discussed but was finally withdrawn from the scope of harmonization at the 2017 Rockville PDG meeting due to the disparity between the three Pharmacopoeias.

As a result, the basic operation procedures described in the JP, EP, and USP are almost similar, but some differences still remain, including the sampling time and judgment limit set out in the "Uniformity of Delivered Dose for Inhalations" and the types of apparatuses and handling of wall losses (inter-stage drug losses) set out in the "Aerodynamic Particle Size Measurement for Inhalations". Discussion about a bilateral harmonization of the "Uniformity of Delivered Dose for Inhalations" between JP and EP is ongoing. In addition, discussion about general tests of uniformity of delivered dose for nasal products has recently started at the newly assembled "Working Group for Nasal Products".

Promoting generic drug utilization and development is an urgent issue for improved use of medical resources; however, generic MDI and DPI products are not available in Japan, in part because there was no officially established guideline or concept paper on evaluation method for bioequivalence testing of inhalations. A Ministry of Health, Labour and Welfare study group established by research funded by the Japan Agency for Medical Research and Development has discussed the requirements to demonstrate bioequivalence of generic DPIs, and announced its "Basic concept on bioequivalence evaluation of generic medicines for dry powder inhalers" in 2016.

This paper essentially follows the concept of FDA's weight of evidence approach, which requires not only in vitro assessment between the two products but also pharmacokinetic and clinical trials data. For in vitro assessment, evaluations of uniformity of delivered dose, fine particle dose, and particle size distribution with stage grouping at multiple test flow rates are required as well as the EMA guideline. Drawing up guidelines for bioequivalence testing of inhalation products not only for DPIs but also MDIs and inhalation solutions would advance further development of inhalation generic products.

Inkjet technology providing for uniform-sized particles

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In the printing industry, controlling toner particle size and ink droplet size jetted by an inkjet head is important for obtaining clear images on paper. For example, toner needs to be controlled to around several micrometres, and ink needs to be controlled to several tens of micrometres, depending on the required image quality. Ink droplet size can be finely tuned by adjusting the nozzle diameter and driving voltage of piezo elements in the inkjet head.

By using an inkjet head instead of an existing spray nozzle such as a rotary atomizer or a two-fluid nozzle in a drying system, we can generate uniform sized solid microparticles. However, inkjet head has not been adopted for mass production of microparticles due to its low productivity.

We propose a new particle generation technology utilizing improved inkjet technology, which we call the fine droplet drying (FDD) process and which can produce powders with narrow size distributions at a high productivity. In addition, we introduce the application example of an inhalable powder generated by the FDD process and a powder handling technique used in the printing industry.

The inkjet head for the FDD process was based on the MH2420 (Ricoh company Ltd.) with an improved nozzle plate that can generate powders of several micrometres with high productivity. Specifically, the discharge hole diameter was 8 µm, with 4 times as many discharge holes as the MH2420. Furthermore, by increasing the driving frequency of the piezo elements, the number of droplets discharged by the FDD process was 40 times as many as discharged by the MH2420.

Utilizing the FDD process, we prepared lactose powder and measured the size distribution. The average size of particles was 3.1 µm, and the calculated span factor was 0.53. In addition, we tried to improve the flowability of the lactose powder by using an additive material which is utilized for toner technique. As a result, the flowability of the lactose powder with the additive was enhanced compared to the original lactose powder.

We then prepared a sustained-release (SR) formulation consisting of salmon calcitonin (sCT) and poly (lactic-co-glycolic) acid (PLGA Resomer® RG502H) using the FDD process. The average particle size of sCT/SR was found to be 3.6 µm, and the span factor was calculated to be 0.65. To make a respirable powder (RP) of sCT/SR (sCT/SR-RP), the fine particles of sCT/SR were mixed with a lactose carrier (Respitose® SV003).

Using cascade impactor analysis, the fine particle fraction of sCT/SR-RP was estimated to be 28%, suggesting that sCT/SR-RP showed fine inhalation property. According to the release profiles of sCT samples in simulated lung fluid, the sCT release behaviour showed a biphasic pattern with initial burst and slow diffusion. After the insufflation of sCT/SR-RP (40 µm-sCT/kg) in rats, the area under the plasma calcium levels-time curve was decreased by 35 % compared with the control-RP group. These results show that FDD technology has promise as a new preparation method for inhalable powders and other pharmaceutical formulations.

Development of inhalable nanoparticles using flash nanoprecipitation

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Flash nanoprecipitation (FNP) is a tool for producing size-controlled nanoparticles with a uniform size distribution. In this study, the FNP was used to produce inhalable nano-matrix particles of cyclosporine A (CsA). CsA nanoparticle-embedded microparticles (nCsAm) were prepared with FNP combined with spray drying with mannitol. The physicochemical properties of nCsAm were characterized, and the anti-inflammatory effects of CsA on airway inflammation induced by ovalbumin (OVA) sensitization evaluated in a rat model after intratracheal administration. Pharmacokinetic behaviour, tissue distributions and side effect- were evaluated after the insufflation of nCsAm (100 μm-CsA/rat).

Laser diffraction analysis found a mean particle size and span factor of the nCsAm of 1.3 μm and 1.4 μm respectively. X-ray powder diffraction and DSC analyses found that the CsA in the nCsAm was in an amorphous state. The nCsAm showed rapid dissolution of CsA in distilled water compared with amorphous CsA. Next generation impactor (NGI) analysis demonstrated fine in vitro inhalation property of nCsAm as evidenced by the fine particle fraction value of 66 %. MMAD and Stdev of the nCsAm NGI data were calculated to be 1.8 μm and 1.7 μm respectively, suggesting that the nCsAm had suitable inhalation properties.
OVA sensitization by intratracheal administration led to significant airway inflammation in rats. On the other hand, intratracheally-administered nCsAm (100 μm -CsA/rat) suppressed antigen-induced inflammatory events in rats, as evidenced by attenuation in up-regulation of myeloperoxidase in bronchoalveolar lavage fluid 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 μm -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 in 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.

IA19L5.1

Aerosol dynamics: let's max-up the dose of the Respimat

Allen Haddrell
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Through understanding, and potentially controlling, the dynamic behaviour of a pharmaceutical aerosol prior to and during inhalation, a cost-effective and simple way to improve the overall drug efficacy can be achieved through minimal changes to the starting formulation. A detailed understanding of pharmaceutical aerosol dynamics can be used in many aspects of product development, ranging from formulation composition and aerosolization through to mouthpiece design.

The hygroscopicity of a pharmaceutical aerosol dictates the evolving size of each droplet during inhalation. Precise resolution of these properties is crucial because of the rapid changes in ambient conditions inherent to inhalation. For example, relative humidity and temperature change rapidly (~0.1 s) during transport from ambient conditions (30 %, 20 C) to the lung (>99.5 %, 37 C). This presentation will describe our recent efforts to characterise the dynamic hygroscopic properties of Respimat aerosol by:

(1) Developing a single droplet analysis instrument, which we named the Electrodynamic Lung (EL), that directly mimics the conditions experienced by an aerosol during inhalation while simultaneously measuring the droplet's size and structure. The conditions in the EL experienced by the aerosol droplet are identical to those experienced by an inhaled pharmaceutical aerosol going from ambient conditions (relative humidity ranging between dry and 8 0%, and temperature ranging from 0 to 20C) to --those in the lung (relative humidity of >99.5 % and a temperature of 37 C).
(2) Measuring the dynamic behaviour of individual pharmaceutical aerosol droplets during the inhalation process.

(3) Modelling the dynamic behaviour of polydisperse pharmaceutical aerosols based on single particle studies.

(4) Predicting the total and regional dose in the lung as a function of various parameters such as the pharmaceutical aerosol starting formulation, initial droplet size, ambient relative humidity, and mouthpiece design. The deposition model is based on the ICRP whole lung model.

(5) Designing a virtual cascade impactor designed to mimic the Next Generation Impactor (NGI) in order to verify predictions of total and regional dose. The virtual cascade impactor study demonstrated a similar deposition profile as the NGI, which validates multiple aspects of this project's design, notably that one can model the deposition pattern of a polydisperse aerosol based on the accurate parameterization of aerosol dynamics collected through the study of an individual droplet.

The whole lung model demonstrated the achievement of significant shifts in total and/or regional dose through changes in initial aerosol size, ambient relative humidity, and solute composition.

IA19L5.2

Critical Quality Attributes comparison between soft mist and pMDIs

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The April 2018 FDA draft guidance regarding the quality considerations of Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) products emphasizes the importance of the device in combination drug products. The container closure system, including the device constituent parts, was listed as a critical quality attribute (CQA) for both MDIs and DPIs, meaning that the device needs to be closely monitored and controlled to ensure product quality and consistency.

A comparison of CQAs for the two most popular MDIs (pMDIs and SMIs) was conducted. Typical CQAs reviewed are delivered dose content uniformity (DDU), spray pattern, plume geometry, and aerodynamic particle size distributions (APSD). Parameters such as spray duration and velocity profiles will also be discussed as quality attributes for SMI. Quantitative results on spray velocity show a typical SMI has less than one third of the velocity, and roughly six times the spray duration compared to a typical pMDI. Control strategies regarding in vitro method development for each product type will be reviewed. For pMDIs, shaking conditions are critical for testing suspension products: incorrect shaking could lead to inconsistent dose delivery, ranging from six times to one tenth the delivered dose of the label claim. For SMIs, environment conditions including humidity influence the performance. Case studies of various SMI products will be presented to demonstrate how to use spray duration and velocity profiles CQAs to control the product quality.

Moreover, a new paradigm, INVIDA (in vitro inhaled drug analysis platform), will be presented as a solution to improve IVIVC (in vitro in vivo correlation). The INVIDA platform includes apparatus which simulate human respiratory physiology, human breathing profiles (healthy vs. disease states), and human respiratory environment (mucus, temperature, humidity, etc.). Using this platform, regional deposition can be studied, and the dynamic performance of the aerosols can be evaluated under different breathing conditions. Testing with the INVIDA system has shown that both the breathing profile and the actuation breathing coordination significantly affect the delivered dose. Data on product performance under different patient-usage conditions will be reviewed in relation to how it predicts in vivo performance.

IA19L5.3

The Respimat® SMI: aerosol generation redefined

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The Respimat® SMI was designed in order to generate an aqueous aerosol for the topical treatment of the lungs. It is a multi-dose device intended for the treatment duration of approximately one month.

The major difference towards other inhalers and at the same time the key challenge is the use of two micro-nozzles which generate an impinging jet. Only the general advances of the semiconductor industry made it possible to produce highly reliable, well-defined micro nozzle systems at affordable pricing. Based on the number of parts the complexity of the device is assessed and is compared with other inhalers.

Based on a long experience in manufacturing the Respimat device to the highest quality standards, it became obvious to listen to the voice of customer and to deliver a re-usable version of Respimat in those markets which value environmentally friendly approaches. The re-usable Respimat has been tested with more than nine cartridges and can be marketed with up to six cartridges considering a safety factor of 1.5. The new re-usable Respimat features an easy-to-read dose indicator on every cartridge. The casing of the dose indicator provides a grip during cartridge replacement.

The Respimat SMI uses a microchip nozzle design which generates the slowly moving aerosol cloud with a MMAD between 4 and 5 μm. While the atomizing principle has been well-known for decades, only its translation into micro-technology ensures a reliable particle size distribution by which the drug load of the droplets can target the deep lung. The uni-axial design of Respimat reduces the space required for the drive assembly including the mechanical spring and tensioning mechanism. Human factor studies have shown that patients can perform all tasks required for using Respimat. In the re-usable version, cartridge exchange was rated as intuitive and simple to manage. Based on their convincing clinical results and good in vitro performance data, the Respimat products are now registered in many countries all around the world.

IA19L6.1

Impact of solid state on inhaled particle dissolution

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The inhalation products market is moving from low dose locally active drugs to higher dosage, poorly soluble and possibly systemically acting compounds. However, the classic pharmacopoeia test for aerosolized products may not be suitable to predict the biological availability of a number of compounds under development, since not just particle deposition, but to an increasing extent the solid state and dissolution properties of the active compounds administered using DPIs and pMDIs will play a crucial role for pulmonary administered drugs.

In the present work, the impact of the solid state of a p38 mitogen-activated protein kinase (MAPK) inhibitor compound designed for the treatment of COPD and asthma has been investigated in rats. Lung and systemic PKs evidence important differences between the crystalline and amorphous solid forms in comparison to the control drug solution. In particular, plasma concentrations after administration of powders are lower compared to those obtained by the pulmonary administration of the drug solution and depend on the solid state of the drug (AUC solution, 46 ng.h.ml-1 > amorphous, 41 ng.h.ml-1 > crystalline, 0.8 ng.h.ml-1). Both the amorphous and crystalline powder drug were found in the lung up to 7 days after administration.

This outcome appears difficult to predict in vitro due to the absence of an established dissolution test able to discriminate the formulation behaviour after deposition. For this reason, RespiCell™, a novel apparatus to investigate the dissolution rate has been developed at the University of Parma. The main features of the RespiCell™ apparatus are that it can be applied to dissolve the fine particles dose collected using a Fast Screening Impactor using a reasonable volume of dissolution medium to maintain sink conditions (170 ml). This system performances have been tested for the dissolution of both soluble and poorly water-soluble APIs present in DPIs on the market. In particular, in the case of tiotropium bromide, a fast dissolving drug, the apparatus evidence an excellent discriminative performance between some test formulations against the reference product (Spiriva® Handihaler®, Boehringer Ingelheim), even if the dissolution time of the API salt is below 15 minutes. The comparisons are carried out applying the notorious difference (f1) and similarity (f2) factors, previously suggested by FDA and EMA guidelines for the comparison of oral dosage forms dissolution profiles.

On the other side, the dissolution of the poorly water-soluble compound indacaterol maleate is completed over a period of 6 hours using a simulated lung fluid containing a surfactant (polysorbate 80, 0.2% w/v). Also in this case, the dissolution profiles of a test product against the reference product (Onbrez® Brezhaler, Novartis Pharmaceuticals) could be compared efficiently using f1 and f2 factors.

It seems timely to design, validate and implement a series of novel experimental approaches specifically tailored for formulations directed to the lungs to complement traditional aerosolization performance studies. RespiCell™ appears to be potentially relevant both for the development of innovative formulation as well as for the development of bioequivalent inhalation products.

How to make a DPI: preparing for Ellipta

Rob Price
University of Bath, UK

The presentation will focus and discuss the key lessons that have been learnt from the generic development of Advair Diskus for the US market and how the challenging scientific and regulatory considerations could be addressed for on-going and future generic drug product development of these complex device/ formulations.

The key points the presentation will cover include:

- What steps are FDA working upon to simplify the path to market for orally inhaled drug products.
- For Q1/Q2 sameness, Q3 similarity requirements for complex ANDAs could vary depending on the product and the need for specialized characterization techniques.
- What have we learnt from the first and second generation of generic Diskus devices?
- Where are we with the development of a robust, discriminatory in vitro release testing (IVRT) approach for orally inhaled drug products.
- Do we need modelling and simulation to support a bioequivalence approach and improve the complex ANDA process?

IA19L6.3

In vivo bioequivalence studies for generic DPIs

Keith Gallicano
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An in vivo bioequivalence (BE) study with pharmacokinetic (PK) endpoints is generally required by regulatory authorities for approval of generic dry powder inhalers (DPIs), particularly when comparative in vitro tests are not deemed sufficient for approval. FDA and Chinese regulators also require a comparative pharmacodynamic (PD) or clinical endpoint study to support BE whereas European authorities require a PD study only if BE is not demonstrated by a PK study. The design and conduct of PK studies (with or without charcoal) is challenging, especially for DPI products containing drugs like salmeterol xinafoate, formoterol fumarate, tiotropium bromide, and glycopyrrolate that can have short time to maximum plasma concentration (Tmax< 10 minutes).

BE studies for these products require frequent blood sampling over the first 10 minutes starting at 1-2 minutes post-dose to reliably capture Cmax; also, adequate blood volume is required to accommodate the low plasma pg/mL concentrations of multiple analytes. Administration of charcoal before drug administration to remove swallowed drug from the GI tract following inhalation can be problematic if not all the charcoal is removed from the mouth/throat before drug inhalation. Inhalation training for subjects participating in PK and PD studies is important to reduce study variability in a BE study. Most DPI products are not highly variable drug products but high PK variability can result from highly variable dose administration procedures that inflate the intra-subject variability in crossover PK studies.
To reduce variability by improving consistency in dosing, subjects should be trained using, for example, an In-Check Inspiratory Flow Meter or placebo test device to inhale study medications at a consistent inspiration velocity to total lung vital capacity, and study staff should administer the doses. One reason why PK studies fail is that it can be difficult to match the test product with a particular reference product if the reference batches are different; studies confirm that Advair 100/50 between-batch variability is large enough to cause issues in PK comparisons.

Bronchodilatation studies using baseline-adjusted FEV1, either as an area-under-the curve (AUC0-xhr, x=4, 6, 12 or 24 hours) following the first dose or as a single time point on the last day of a 4-week treatment, as the primary endpoint is the basis for all PD studies of DPIs for FDA. For short-acting beta-2 agonists (albuterol DPI), FDA recommends a dose-scale (Emax model) analysis of the endpoints and also allows a bronchoprovocation (methacholine challenge) study as an alternative to the bronchodilatation study using either provocative methacholine concentration or dose that causes a 20% decrease in FEV1 relative to post-saline FEV1 as the endpoint. Though a bronchoprovocation study has more sources of variability (DPI inhalation, spirometry procedures, and methacholine inhalation) than a bronchodilatation study (DPI inhalation, spirometry procedures), the former may provide a more sensitive means of demonstrating BE between a test and reference albuterol DPI product.

This presentation will review the challenges in design, conduct, and data analysis of PK and PD BE studies for generic DPIs.

Poster abstracts

IA19P01

Inhaled combination phage-antibiotic therapy for antimicrobial resistance bacteria

Yu Lin
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Pseudomonas aeruginosa is a major cause of morbidity and mortality in patients with cystic fibrosis, chronic obstructive pulmonary disease, bronchiectasis and sepsis. Bacteriophages (or phages) and antibiotics can potentially show synergistic antimicrobial effect on antimicrobial resistance bacteria. Inhalation delivery of synergistic phage-antibiotic combination might have better local drug bioavailability and efficiency against microbes residing in the airways.

We investigated antimicrobial effect of phage PEV20 in combination with ciprofloxacin, tobramycin, colistin, aztreonam and amikacin against P. aeruginosa strains isolated from cystic fibrosis patients. PEV20 and ciprofloxacin exhibited the most synergistic effect on two clinical strains FADD1-PA001 and JIP865. Air-jet and vibrating mesh nebulizers were used for the aerosol generation of phage PEV20-ciprofloxacin combinations containing 1/4 and 1/2 of the minimum inhibitory concentration of ciprofloxacin against strains FADD1-PA001 and JIP865, respectively.

The synergistic antibacterial activity was maintained after nebulization by both nebulizers. Inhalable droplets generated by air-jet nebulizer was smaller and the span was slightly larger than vibrating mesh nebulizers. The fine particle fractions (FPF) were 68 % -69 % and 51 % - 53 % for the air-jet and vibrating mesh nebulized aerosols, respectively. Dry powder inhaler provides better patient compliance and handling characteristics compared with nebulization. Therefore, ciprofloxacin and PEV20 were co-spray dried using L-leucine with or without lactose as excipients. Liquid feed was made up of 18 mL of ciprofloxacin with excipients in ultra-pure water and 2 mL of PEV20 suspension. The mass ratios were set at 1:1:1 for ciprofloxacin, lactose and L-leucine (Formulation A) or 2:1 for ciprofloxacin and L-leucine without lactose (Formulation B). PEV20 were set at 108 and 109 PFU/mL for FADD1-PA001 and JIP865, respectively. Formulation A formed nearly spherical and hollow particles with dimpled surfaces. The particle morphology of formulation B was hollower and more corrugated. Powders were characterized as partially crystalline and both recrystallized at relative humidity higher than 40%. In vitro bactericidal synergy was remained intact after dispersion using both low and high resistance OsmohalerTM for the two powders. Powder aerosol performance was measured using next generation impactor in low resistance inhaler at 100 L/min and by multi-stage liquid impinger in high resistance inhaler at 60 L/min. FPF from NGI were 59.7 ± 2.1 % and 64.3 ± 2.9 % for A and B, respectively. FPF obtained from MSLI were 71.0 ± 3.4 % and 73.3 ± 5.0 %, respectively

In conclusion, inhaled phage PEV20 and ciprofloxacin combination showed promising antimicrobial and aerosol characteristics for potential treatment of respiratory tract infections caused by drug-resistant P. aeruginosa.

IA19P02

In vitro study of nebulized endolysin Cpl-1 against Streptococcus pneumoniae

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Pulmonary delivery of antimicrobials has been proven to be more effective than oral and intravenous administration for the treatment of lung infections because inhalation therapy is targeted to the respiratory system directly for local effect instead of systemic treatment. It has been reported that nebulized endolysin Cpl-1, a protein derived from a bacteriophage with antibacterial properties, exhibits strong efficacy in vitro [1] and in vivo [2] against Streptococcus pneumoniae lung infections. However, the stability of Cpl-1 after aerosolization using commercial nebulizers has not been examined. The aim of this study was to investigate the in vitro efficacy and aerosol performance of nebulized endolysin Cpl-1.

Air-jet and vibrating mesh nebulizers (Pari LC Sprint jet nebulizer with Pari Boy SX Compressor and Pari eFlow Rapid vibrating mesh nebulizer) were used to aerosolize endolysin Cpl-1 (40 µg/mL) formulated in phosphate-buffered saline. Air-jet nebulized samples were collected after 7, 14, and 21 min respectively. The activity of Cpl-1 was tested before and after nebulization using a turbidity reduction assay [3]. Droplet size distribution and fine particle fraction (FPF, %wt of particles< 5 µm in the aerosol cloud) were measured by laser diffraction. Live imaging videos using 3D Cell Explorer were taken to observe the bioactivity of nebulized Cpl-1.

A significant reduction of Cpl-1 activity was observed over time when the endolysin was aerosolized with the air-jet nebulizer. Seven minutes after the start of nebulization, the activity of Cpl-1 was reduced by 51 %, followed by 73 % and 93 % after 14 min and 21 min respectively. In comparison, Cpl-1 remained relatively stable with only a 24 % activity loss when aerosolized by vibrating mesh nebulizer. Live imaging videos confirmed the reduced activity of Cpl-1 after nebulization. The particles generated by the air-jet nebulizer (4.8 ± 0.1 µm) were slightly smaller than those generated by the vibrating mesh nebulizer (5.3 ± 0.3 µm). The FPF values were 52.3 ± 1.6 % and 46.1 ± 3.3 % for the air-jet and vibrating mesh nebulized aerosols, respectively.

Aerosolization by a vibrating mesh nebulizer maintained the antimicrobial activity of Cpl-1, whereas nebulization by an air-jet nebulizer caused significant loss. Both nebulizers generated aerosol particles suitable for delivery by inhalation. This study showed that a vibrating mesh nebulizer could potentially be used to deliver endolysin for inhalation therapy of respiratory infections.

IA19P03

Immunomodulatory effects of Simvastatin Nanoparticles Inhaler Formulation for Chronic Pulmonary Diseases

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Simvastatin (SV) is a hypolipidemic drug that acts by inhibiting the HMG-CoA reductase enzyme. There is increasing evidence to show that SV possesses antioxidant, muco-inhibitory, and anti-inflammatory properties that could be valuable in reducing pathological conditions usually found in chronic pulmonary diseases. However, the benefits of SV are hampered by its low water solubility, rapid systemic clearance, rapid degradation of SV into simvastatin hydroxyl acid (SVA) resulting in low bioavailability, and subsequent sub-therapeutic levels of drug in the lung.

This study focuses on the development of a stable SV nanoparticle (SV-NP) formulation for inhalation that could potentially be used as a treatment for inflammatory respiratory diseases. SV-NPs coated with PLGA and pluronic-F127 as stabilisers were prepared using a solvent/antisolvent precipitation method. The formulation was characterised in terms of particle size, physico-chemical stability, and in vitro aerosol performance. The SV-NP formulation was also evaluated for its ability to decrease oxidative stress, i.e. nitric oxide -NO – production, using an inflamed alveolar macrophages cell model, following stimulation with 1 ng/mL of lipopolysaccharide (LPS), after 6 and 24 hours. Furthermore, the formulation was assessed for its muco-inhibitory effect on an established air interface lung epithelia Calu-3 cell model.

Results showed that the SV-NPs were found to have an average diameter of 254±12 nm and were stable up to 9 months. Fine particle fraction (FPF) was calculated as a percentage of SV from the regression of log-linear plots of stage-size versus cumulative stage deposition, corresponding to the cut-off size ≤ 5 µm. The SV-NP formulation's particle size was suitable for inhalation therapy, with a fine particle fraction of 42.59 ± 7.14 % after 9 months of storage at 4° C. No statistical difference was found between the SV-NP formulation, control formulations, and untreated cells 6 hours after SV deposition, while a significant difference was found for the SV-NPs after 24 hours. This is most likely due to the sustained release of the drug from the SV-NPs, which led to improved antioxidant activity. Additionally, the mucus inhibition study demonstrated the ability of the SV-NP formulation to reduce mucus production on Calu-3 cells compared to the untreated controls at day 14.

The simvastatin nanoparticle formulation has proven to decrease oxidation stress and mucus production in lung cells. This therapy could potentially be used for the localised treatment of pulmonary diseases, where oxidative stress and hyper mucus production is a component that drives disease progression

IA19P04

Production and characterization of spray-dried budesonide from organic solvent suspensions

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Spray drying of suspensions containing crystalline hydrophilic particles could avoid production of amorphous hydrophilic material and allow hydrophilic particles to be coated with a protective layer of a hydrophobic drug. However, the drug/excipient ratio on each agglomerate after spray drying will not be uniform since the number and volume of suspended particles enveloped by the droplets depend on both the droplet and particle size distributions, the size ratio of droplets to particles, and the suspension concentration.

We built a simulation model to simulate how suspended particles are distributed among the droplets, and the drug and excipient ratios in various aerodynamic particle size fractions were measured to verify the model. The suspension formulation contained 0.7 mg/ml dissolved budesonide (BUD) and 12 mg/ml suspended crystalline lactose particles (Lactohale 300) in isopropanol alcohol (IPA). The volume median diameter (VMD) and geometric standard deviation (GSD) of the lactose particles were 4.79 µm and 2.37 µm, respectively.

A Buchi-290 spray dryer was employed to produce powders at an inlet air temperature of 70 °C and 100 % aspiration flow. Different atomization and liquid feed rates of the two-fluid nozzle were used to generate different VMDs of droplets (5, 16, 25, 32 µm) with a GSD of 1.8. The powders were aerosolized into the Next Generation Impactor (NGI) at 100 L/min using Aerolizer.

For the simulation, the major operating parameters included droplet VMD (5, 10, 20, 30, 40 µm), GSD (1.00, 1.25, 1.50, 1.75, 2.00), and suspension concentration (Cs) (0.5, 5% v/v). The percentage of empty droplets with no suspended particles and the agglomerate size distribution were examined. The change of BUD/lactose mass ratio in the bulk powder decreased from 86.2 % to 67.1 % as the droplet VMD decreased from 32 µm to 5 µm.

Scanning electron microscopy showed the presence of small spherical particles, which were probably generated from empty droplets, as well as tomahawk-shaped lactose particles. Small empty droplets would produce particles that were too small to be collected. As a result, the overall BUD/lactose proportion was lower than expected. Furthermore, the smaller the droplet VMD, the smaller the particles produced, leading to more uncollected drug and hence a lower BUD/lactose mass ratio.

Moreover, for powder generated from the VMD of 25 µm, the changes of BUD/lactose ratios among different sized particles were non-uniform and significantly increased from 42 % to 2062 %, with decreasing aerodynamic particle size from 3.4 µm to 0.4 µm after dispersion under droplet VMD of 25 µm.

In the simulation, the percentage of empty droplets decreased from 87.0 to 1.6 % with increasing droplet VMD and from 5 µm to 40 µm under a droplet GSD of 1.75 % and Cs of 5 %. Increasing the suspension concentration would also decrease the percentage of empty droplets but would increase the size of the agglomerates. These findings are important for using and optimising spray drying suspensions containing dissolved compounds.

IA19P05

In-vitro comparison of deposition pattern in idealized throat models using Advair® Diskus® and Asaris® inhalation powder

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In vitro comparison for mouth throat deposition in USP Induction port and Alberta idealized throats (child and adult version) was investigated. Deposition patterns of drug substance were studied using commercially available Advair® Diskus Inhalation Powder 100/50 (USA) and Asaris® Inhalation Powder 100/50 (Europe). The study was carried out using the Next generation Impactor and the samples (n=3) were analysed using High performance liquid chromatography.

For Advair® Diskus® 100/50, the percentage of drug deposition of salmeterol were found to be 14.59 % (SD±0.30) for the USP throat, 19.65 % (SD±0.53) for the child idealised throat, and 18.38% (SD±1.08) for the adult AIT. The drug deposition of fluticasone propionate were found to be 14.56 % (SD±0.20) for the USP throat, 21.87 % (SD±0.41) for the child AIT, and 19.11 % (SD±1.19) for the adult AI. The ISM was calculated on the basis of delivered dose in percentage. Averages ISM (%) for salmeterol were 28.64 %, 26.14 % and 25.40 % for USP traditional throat, child idealised throat and adult idealised throat respectively. The average ISM (%) for fluticasone were 31.38 %, 28.05 % and 27.94 % for the USP traditional throat, child idealised throat and adult idealised throat respectively.

For Asaris® Inhalation Powder 100/50, the percentage amounts of salmeterol drug deposition were 15.41 % (SD±1.05), 21.18 % (SD±0.43) and 18.89 % (SD±1.79) for the USP traditional throat, child idealised throat and adult idealised throat respectively in Asaris. Similarly, the percentage amount of drug deposition of fluticasone propionate were 16.30 % (SD±1.16), 25.24 % (SD±0.56) and 21.88 % (SD±1.80) for the USP traditional throat, Child idealised throat and Adult idealised throat respectively. The ISM averages (%) for salmeterol were 35.24 %, 37.37 % for the USP traditional throat, child idealised throat and adult idealised throat respectively, and for fluticasone these were 34.94 %, 34.06 % and 35.51 % for the USP traditional throat, child idealised throat and adult idealised throat respectively.

In both idealised throat models, the percentages of drug deposition for both APIs were higher than in the USP induction port, whereas deposition of fine particles were lower. This deposition difference between USP and more realistic throat profiles hints that the latter might lead to more accurate in vitro -in vivo studies predictions.

IA19P06

Functionalised dextran particles for overcoming antimicrobial resistance

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Conferring biocompatibility and biodegradability to particles is vitally important for drug delivery as this prevents potential problems with bioaccumulation of by-products. As a biodegradable polymer, dextran (a polysaccharide consisting predominantly of 1,6-glucosidic linkages) is very attractive because it is already widely used in commercial drug formulations. In this work, dextran has been functionalised with acetal and aldehyde functionalities, and acetalated dextran was used as an acid-responsive material for preparing biodegradable particles for drug delivery using emulsion method. Aldehyde groups were also introduced to dextran to the attachment of therapeutic agents, including bacteriophages and antibiotics, onto the prepared particles.

This study aims to develop novel formulations in the form of particles for the controlled delivery of combined bacteriophages and antibiotics, which would be more effective for the treatment of chronic lung infections than the single entity. The functionalised material was fully characterised by using solid state and liquid NMR methods. After confirming the successful synthesis of functional dextran, the material then was used to prepare the particles using emulsion method. The particles were characterised by SEM and laser diffraction technique. The further conjugation of phages and antibiotics was characterised by using NMR and FITR.

The following nine groups (n=10 per group) were used to assess biofilm dispersal and biofilm viability of Pseudomonas aeruginosa:

1. Control cells
2. Antibiotic
3. Phages
4. Phages and antibiotic
5. Dextran particles
6. Antibiotic loaded Dextran particles
7. Phage loaded Dextran particles
8. Phages and antibiotic Dextran particles
9. PBS only

Biofilm dispersal of Pseudomonas aeruginosa biofilm after being exposed with the treatments was determined by crystal violet staining. For viability measurements, the BacTiter-Glo Microbial Cell Viability Assay, which is based on the quantitation of ATP present in bacteria by using a thermostable luciferase and which is known to correlate to viable cell counts, was used. Confocal microscopy was used to visualise biofilm dispersal and bacteria viability. P. aeruginosa biofilms were grown in glass-bottom, 24-well plates (MatTek Corporation, Ashland MA, USA) as described above and, after treatment, biofilms were stained with LIVE/DEAD® BacLight™ bacterial viability kit reagents. In addition, the cytotoxicity of particles was assessed on human fibroblast cells (MRC-5) using an Alamar Blue assay, which measures the ability of living cells to reduce redox dye (resazurin) into a fluorescent dye (resorufin).

IA19P07

In vitro aerosol performance of originator and generic fixed-dose combination metered dose inhalers

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Inhaled corticosteroids and long-acting beta-2 agonists are commonly used to treat asthma and chronic obstructive pulmonary disease. Fixed dose combination inhaler products containing these two types of drugs are available as both metered dose inhalers (MDIs) and dry powder inhalers (DPIs). Over time, generic products have emerged after the expiry of the originator product patents.

Although in vivo pharmacokinetic and pharmacodynamic studies of originator and generic inhalers have been published over the years, there are still few reports comparing the in vitro aerosol performance of these products. Such studies are needed to yield published data that could be useful for guiding quality assessments and in vitro-in vivo correlation of fixed dose combination products.

The objective of this study was to compare the in vitro ex-valve dose and fine particle fraction (FPF) of an originator and a generic combination MDI. Two Seretide 250/25 MDIs (GlaxoSmithKline, Australia) and two fluticasone + salmeterol 250/25 Cipla MDIs (Cipla Australia, Australia) were tested. The labelled doses were 250 µg fluticasone propionate (FP) and 25 µg salmeterol (equivalent to 36.25 µg salmeterol xinafoate (SX)), with 120 metered doses per inhaler.

The life of each inhaler was divided into 3 phases of 40 doses each: beginning, middle, and end. Within each phase, 10 doses were randomly selected for ex-valve dose measurement, and 3 doses were randomly selected for FPF measurement. The ex-valve dose and FPF were determined by actuating one puff into a Dosage Unit Sampling Apparatus and a Next Generation Impactor (NGI), respectively.

The mean ex-valve doses of FP and SX throughout the lives of both products were within 85.0 %-115.0 % of the stated dose, the range specified in the BP, except that one of the Cipla MDIs generated less FP and SX in the end phase (81.6 % and 84.6 % of the labelled dose, respectively (n = 10), which may be due to the tail-off effect that occurs near the end of the life of MDIs. Both products met the BP requirement for dose uniformity in all phases of their lives.

The Seretide MDI demonstrated consistently higher FPFs than the Cipla MDI for both drugs throughout the lives of the inhalers, which was complemented by higher throat deposition in the NGI for both drugs from the Cipla MDI. The FPFs of FP from Seretide and the Cipla MDI were 39.9 % vs 30.1 % in the beginning phase, 38.5 % vs 28.5 % in the middle phase, and 39.6 % vs 26.7 % at the end of the inhaler (n = 6). Similarly, the FPFs of SX in those phases were 39.3 % vs 30.6 % in the beginning phase, 35.6 % vs 28.7 % in the middle, and 37.5 % vs 26.4 % at the end (n = 6).

The lower FPFs in the end phase of the Cipla MDI might be related to the tail-off effect mentioned above. The difference between the FPFs of the two products and the implication of that difference for their clinical effects of those MDIs require further investigation.

IA19P08

"Intentionally" made amorphous substance to quantify "unintentionally" produced amorphous materials: Decades of hands-on experience

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Amorphous content determination is an essential aspect of characterising micronised particles for dry powder inhaled products. It is well understood that, milling-induced disordered (amorphous) material is highly energetic and a considerable portion of these particles significantly influences the cohesive and adhesive balance (CAB) of micronised particles. This behaviour results in varying fine particle fraction (FPF) which ultimately affects dry powder inhaler (DPI) performance. It's reasonable for the regulatory authorities (e.g. FDA, MHRA) to seek a suitable analytical method to quantify amorphous content, control over amorphous materials, and they may assign limits for amorphous content in batches that are to be used for commercial purposes.

Solution calorimetry (SolCal), gas perfusion microcalorimetry (GPC) and dynamic vapour sorption (DVS), arguably, are the most sensitive techniques for quantifying amorphous material within processed samples. The "Pros and Cons" for using these techniques are outlined below.

SolCal - Pros: a) Flexibility in mass, solvents, temperature range and vessel sizes (e.g. Fluticasone, Formoterol, Salmeterol, Tiotropium bromide monohydrate (TBM). b) No effect of particle size and shape measures any sample that's inside the ampoule. c) No mixing or blending required. Cons: a) Volatile solvents (e.g. acetone, IPA) can't be used. b) Different sealant for some solvents (e.g. DCM, THF). c) All experimental processes demand to be precise. d) Offer challenges if heat of solution is <20J/g between crystalline and amorphous materials.

GPC - Pros: a) As heat is ubiquitous, any changes in power (μW) can be measured effectively for very small changes in sample. b) No mixing or blending required. c) Flexible temperature range. Cons: a) Limited solvents (DI Water, Ethanol) can be used. b) Hydrates, solvates (either initially present or formed during experiment) possess challenges in interpretation (e.g. Salbutamol, TBM). c) High mass can result in non-uniform vapour exposure. d) Effect of particle size and shape can't be ruled out, especially at wetting process. e) Long run time (e.g. 24 hours).

DVS-Advantage - Pros: a) Flexibility in mass, solvents (e.g. ethanol for fluticasone, TBM), temperature range and sample pan. b) Recrystallisation (weight loss phenomenon) directly proportional to amorphous material present in the sample. c) No mixing or blending required. Cons: a) Hydrates, solvates (either initially present or formed during experiment) possess challenges in interpretation (e.g. TBM). b) Effect of particle size and shape can't be ruled out, especially at adsorption/absorption process. c) Volatile solvents (e.g. acetone) may not maintain %RVP accurately. d) Long run time (e.g. 24 hours).

It is essential to understand the process of detecting small levels of amorphous material and having control over this material is critical. Obtaining reproducible data and understanding the processes for these challenging systems (crystalline, amorphous, hydrate, solvate, milled, micronised samples etc.) and their responses to each specialised technique requires in-depth knowledge, skills and experience.

IA19P09

Inhalable nanocarriers for long-lasting effects of drugs in the respiratory system

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Retention of inhaled drugs in the respiratory system is desirable for effective treatment of respiratory and lung diseases; however, inhaled particles are rapidly cleared toward the pharynx by mucociliary clearance (MCC). A number of efforts have been undertaken to develop inhalable nanocarriers (iNCs) with pulmonary retention. This study was undertaken to develop iNCs with excellent retention in the respiratory system using a mucosal drug delivery system (mDDS) approach, which could be a promising strategy for iNCs that would avoid MCC.

P2, an aggregation-caused quenching (ACQ) probe, was used as an environment-responsive dye for reliable fluorescence imaging on iNCs specifically. ACQ effect and rekindling of P2 were evaluated in simulated lung fluid (SLF). P2-loaded iNCs were prepared by flash nanoprecipitation and coated with a neutral polymer (iNCs/N) for mucopenetration and with a cationic polymer (iNCs/C) for mucoadhesion.

Prepared iNCs were evaluated in terms of physicochemical properties and in vivo fate in rats after intratracheal administration. The fluorescent intensity of P2 in acetonitrile solution was found to decrease abruptly when the ratio of SLF to acetonitrile reached 55 %, and marked rekindling of quenched P2 was not observed in SLF. These properties suggest the applicability of P2 to imaging of insufflated iNCs with limited pseudo-positive interference.

Both iNCs had a mean diameter of approximately 150 nm with narrow size distribution and high dispersion stability in SLF up to 6 hours. The iNCs/N and iNCs/C possessed zeta-potential of approximately 4 mV and 40 mV, respectively. Quartz crystal microbalance analysis indicated that mucin-particle interactions for iNCs/C were stronger than those for iNCs/N, possibly due to potent electrostatic interactions between mucin and the positively-charged surfaces of iNCs/C.

In a diffusion test using artificial mucus, mucodiffusiveness was found to be higher in iNCs/N with limited interactions toward mucin, and mucin-particle interactions for iNCs/C might be a part of reason of decreased mucopenetration. From these findings, iNCs/N and iNCs/C would possess mucopenetrating and mucoadhesive properties, respectively.

Confocal laser scanning microscopic images of the sectioned lungs showed that intratracheal iNCs/N were distributed homogeneously across the respiratory surfaces, suggesting rapid penetration within the mucus layer. Insufflated iNCs/C were present in clumps and might have been trapped in the superficial mucus layer. Images of whole lungs with in vivo imaging system showed that mucoadhesive iNCs/C were cleared toward the pharynx. By contrast, mucopenetrating iNCs/N displayed better pulmonary retention, and this result might be attributable to their avoiding MCC in the respiratory system.

In conclusion, mucopenetrating formulations for inhalation would offer enhanced drug exposure to the disease site of respiratory and lung diseases, resulting in better clinical outcomes.

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