FORMULATION & DELIVERY

SERIES UK 2019

Pre-Event Newsletter Mar 2019

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ILEC CONFERENCE CENTRE

29 - 30 APRIL 2019 | LONDON, UK

OXFORD GLOBAL CONFERENCES

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Conference Producer: Inhalation

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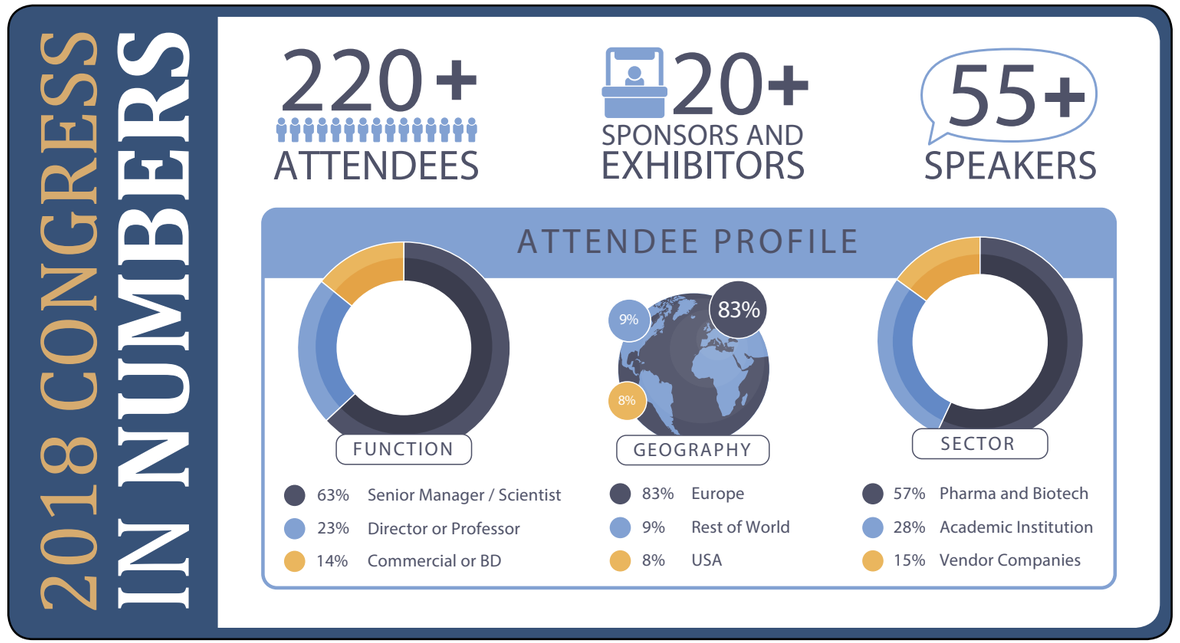


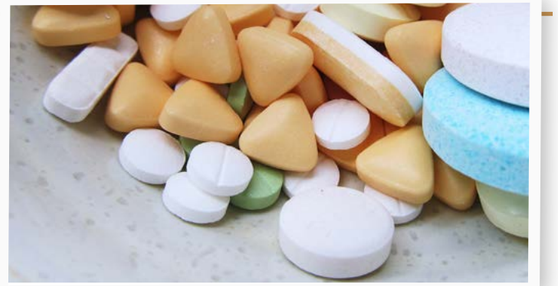
WELCOME TO OXFORD GLOBAL'S FORMULATION & DELIVERY SERIES UK PRE-EVENT NEWSLETTER!

With the 5th Formulation & Drug Delivery Congress and co-located 4th Inhalation & Respiratory Drug Delivery Congress taking place in April this year in London, I am delighted take to look back at the 2018 event and provide some exciting details on a few of the key features & new additions for the 2019 congress.

The 2018 event brought together over 250 attendees to discuss large and small molecule drug formulation and delivery and examine development & formulation of inhaled therapies as well as novel inhalation devices and analytics. 2018 also saw the launch of the breakfast roundtables, with attendees advising the opportunity to discuss key challenges and knowledge share with their peers was invaluable.

The Formulation & Drug Delivery Congress 2019 will again ensure delegates gain invaluable insights into both large and small molecule formulation development as well as drug delivery. New for this years programme is the expansion of the programme to include continuous manufacturing, bioanalysis and stabilisation updates, and featured streams on RNA and Nanoparticle-mediated formulation and delivery.

At the 4th Inhalation & Respiratory Drug Delivery Congress, alongside the popular 2018 topics in novel inhalation and devices, in line with current industry trends, our 2019 event will examine further aerosol science & particle engineering updates as well as alternative therapeutic fields such as inhaled vaccines, antibiotics and insulin.



For 2019, the roundtables will make a return enabling you to knowledge share and discuss hot topics with other experts in your industry. Alongside this, 2019 will see the launch of the event app providing you with an easy way to keep up to date with the conference programme, networking events and reach out to your peers through the messaging system!

After a full day of learning, knowledge sharing and meeting new people, what better way to unwind after the first day of the congress than with a glass of wine (or two) at Oxford Global's networking drinks.

Read on for a range of interesting interviews and insights with some of this year's industry-leading speakers and participating sponsors, and we look forward to welcoming you to the 2019 Congress in April!

- Hayley Watson, Portfolio Director

ILEC CONFERENCE CENTRE

29 - 30 APRIL 2019 | LONDON, UK

5TH ANNUAL
FORMULATION & DRUG DELIVERY
CONGRESS

co-located with

4TH ANNUAL
INHALATION & RESPIRATORY DRUG DELIVERY
CONGRESS

WHO IS ATTENDING?

For the full attendee list please contact
marketing@oxfordglobal.co.uk

- **350+ senior level attendees** from leading pharmaceutical, biopharmaceutical, biotechnology, diagnostics, CRO and solution provider companies.
- **Professors, Directors and Heads** of formulation development and drug delivery, biologics developments, inhalation drug delivery, respiratory pharmacology, inhalation process development, inhaled dosage forms, pulmonary disease, respiratory therapeutics.
- **Highly esteemed members** of academic and government institutions.

These companies and many more:

GlaxoSmithKline · Novartis · AstraZeneca · Janssen · Genentech A Member of the Roche Group · abbvie · Savara · Alnylam Pharmaceuticals · Boehringer Ingelheim · Bayer · UCB · King's College London · Takeda

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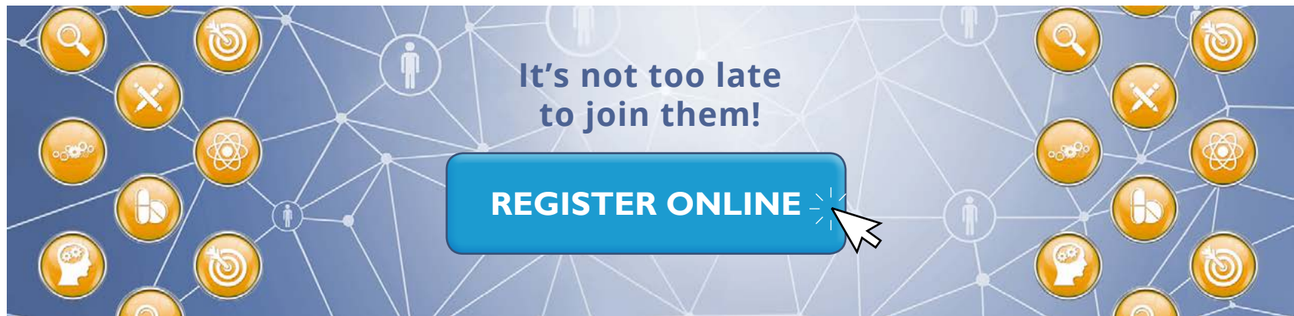


RECIPHARM: THE BRIGHTEST MINDS IN THE CDMO INDUSTRY

ADITYA DAS

Aditya Das,
Director of Business Development, Recipharm AB

Aditya Das is a Director of Business Development at Recipharm AB focused on inhalation drug product development and commercialisation for global clients. As a Business Development professional serving the pharmaceutical industry, Dr. Das coordinates the interface between client needs and external services/ capabilities to facilitate strategic positioning for optimal product development and global registration. Services provided to clients in response to specific requests include regulatory input (chemistry, manufacturing and control sections), risk analysis, cost estimates, process design, and combination (drug/device) product development for both small and macromolecules.

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK, and the US, and are continuing to grow and expand our offering, for our customers.

Employing around 6,000 people, we are focused on supporting pharmaceutical companies with our full service, taking products from early development through to commercial production. For over 20 years we have been there for our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again.

We provide support to pharmaceutical companies of all sizes with their outsourcing requirements, with our company operating in two core areas.

Contract development services

Our development & technology segment offers clients a comprehensive range of services, with the aim of supporting the customer from the initial product concept to the approved pharmaceutical drug, in some cases, through various forms of risk sharing. We can offer both experience and expertise in various services including:

- Inhalation Formulation Development
- Drug Substance Development
- Drug Product Development
- Analytical Chemistry
- Clinical Trial Material

Contract manufacturing services

Recipharm's largest business stream is manufacturing services. Our pharmaceutical manufacturing expertise means we can deliver a large number of pharmaceuticals in a variety of dosage forms requiring the use of a broad range of technologies, including:

- Solids
- Semi-solids
- Liquids
- Inhalation
- Injectables
- Ophthalmics

As part of our manufacturing services, we also provide our customers with a comprehensive packaging service in a large number of variants.

We also help our customers by simplifying their processes and managing complexities. We do this by offering additional services such as quality assurance, regulatory services, and logistics solutions, including Vendor Managed Inventory (VMI).

For many of our clients that utilise our manufacturing capabilities, it is important that we have a solid foundation in drug development. We are proud to possess a broad pharmaceutical expertise that is essential in developing and supplying drug products.

Through an integrated knowledge exchange between Recipharm's manufacturing and development units, the skills and experience we have are used to improve the development organisation. Furthermore, this operating model helps to achieve a degree of efficiency and ensures quality when a pharmaceutical drug transitions from the development phase through to the manufacturing phase.

Inhalation services

Recipharm offers an end-to-end service for inhalation products from early stage development through to commercial manufacturing. Our dedicated inhalation team has the depth of knowledge required to both understand and overcome the challenges associated with developing and manufacturing inhalation products and overcoming hurdles to help speed up time to market.

With more than 20 years of experience our inhalation development site in Research Triangle Park specialises in the formulation and characterisation of inhalation products supporting various dosage forms for new chemical entities (NCEs) and generics.

Our modern, well-equipped facility in Holmes Chapel offers manufacturing, packaging and warehousing facilities for inhalers and nasal sprays as well as end-to-end quality control, GMP compliancy and IMP licence for clinical supplies.

As our global footprint grows, we continue to conduct our business as we always have, managing complexity and delivering value for money with each customer's needs firmly at the heart of all that we do. That's the Recipharm way ■

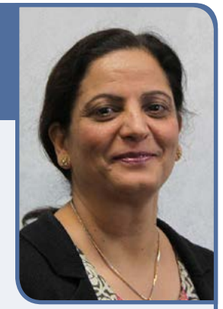
Aditya will be presentating at the Formulation & Delivery US Series on 18th March with his talk *'Inhaled Drug Product Development and Commercialization Using A 505(b)(2) Regulatory Pathway'* and also at the Formulation & Delivery UK Series on 29th April with his talk *'Transmucosal Drug Delivery To The Brain Via The Nose'*.

TARGETED HYBRID NANOPARTICLES FOR DRUG DELIVERY TO BRAIN

SHILPA PAWAR, JANE ELIZABETH ALDER, KAMALINDER K SINGH

School of Pharmacy and Biomedical Sciences, Faculty of Clinical and Biomedical Sciences, University of Central Lancashire

KAMALINDER K SINGH,
Professor, University of Central Lancashire



Kamalinder leads the Nanomedicine and Innovative technologies research group at UCLan within the faculty of Clinical and Biomedical Sciences at University of Central Lancashire. With more than 30 years experience in academia, her research interests are in the field of advanced drug delivery and drug targeting with focus on formulation design and development, and evaluation of different biocompatible nanoparticle-based platform technologies including protein, lipid and hybrid nanoparticles and exploiting them to deliver drugs across various biological barriers.

The central nervous system (CNS) poses a unique challenge for drug delivery. The existence of blood–brain barrier (BBB) hampers the effective treatment of CNS diseases. Almost all macromolecular drugs and more than 98% of small molecule drugs including neurological drugs, anti-cancer agents, antibiotics, etc. cannot pass the BBB. The BBB is a brain-specific, selective barrier that regulates the transport of substances between the circulation and the brain. The barrier properties of healthy BBB are mainly due to the presence of tight junctions between the endothelial cells, which are steadily maintained by astrocytes and pericytes. Further anatomical features, such as abundant presence of multidrug resistance proteins, e.g., P-glycoprotein (P-gp) and multidrug resistance proteins (MDRPs), can prevent drug accumulation inside the brain; as a result, the administered drugs remain unsuccessful or cannot achieve the wanted physiological effect. Thus, BBB being the bottleneck in the medication of CNS diseases is primary focus in the development of novel CNS drug delivery techniques. Nanotechnology offers the possibility to deliver small molecules/drugs against CNS disorders across BBB.

The incidence of neurodegenerative diseases and aggressive brain cancers is continually growing. Glioblastoma multiforme (GBM) is one of the most aggressive and deadliest CNS tumours and is classified as grade IV malignant tumour. Standard treatment for GBM consists of surgical resection, radiotherapy and temozolomide as adjuvant and concomitant chemotherapy. The only approved chemotherapeutic agents for GBM treatment are temozolomide (oral and I.V), carmustine (I.V and implants), lomustine (oral). Even after massive progress in the therapeutic field, the survival rate is notably low (15-18 months) making GBM treatment a big challenge. Though GBM patients show variable/partial and heterogeneous BBB disruption but have regions with intact BBB, which is sufficient to limit drug access to tumour cells. Additionally, BBB disruption does not necessarily imply loss of other biological mechanisms such as efflux transport system which hamper drug delivery across BBB.

We have developed safe and biocompatible hybrid nanoparticle-based platform technology for delivering CNS negative drugs across the BBB using commercially available and scalable processes. These nanoparticles have been suitably appended with VEGF targeted ligand for targeting to GBM. The presentation will discuss the Quality by design development of these novel biomimetic protein-lipid hybrid nanoparticles. A critical and important requirement for nanoparticulate brain delivery systems is that they are rapidly biodegradable, i.e. over a time frame of a few days. Hybrid nanoparticles being fabricated from endogenous materials are free from challenges of toxicity and immunogenicity which polymer based nanodrugs face due to their accumulation in brain. Nanoparticle formulation has been optimized for product and process parameters using rotatable central composite design to assure that the critical quality parameters, particle size, polydispersity index, entrapment efficiency and total drug are within the specified limits and meet the quality target product profile.

Hybrid nanoparticles showed more than seven times higher permeability than the free cytotoxic drug when tested using a 3D *in-vitro* BBB model with no active efflux of nanoparticles. The nanoparticles showed preferential targeting followed by concentration and time dependent uptake by U87MG GBM cells with improved efficacy. These nanoparticles hold promise in future GBM treatment and the platform technology opens translational avenues for the challenging task of drug delivery in CNS therapeutics ■

Kamalinder will be expanding on this topic at our 5th Annual Formulation & Drug Delivery Congress as part of our Formulation & Delivery Series UK.

Hear her presentation *'Nanoparticle-Mediated Formulation For Brain Delivery'* on Day Two in the stream *'Nanoparticle-Mediated Formulation And Drug Delivery'*.

INJECTION PAIN OF BIOLOGICS - DOES IT HURT?

JONAS FRANSSON

Taking an injection may be an uncomfortable, frightening or painful experience, but it may also be a "no-big-deal" event with no negative feelings involved at all. For not so few people taking and feeling an injection is a signal and re-assurance that they have received the medication that keeps them well and it generates positive feeling. I have heard this from people ranging from haemophilia to cancer to diabetes. However, there are still many facets of injections that most people have some concerns with.

The intrusive nature of an injection involves many components and events.

Injection type: Typically physicians rate the "painfulness" of injections in the order Intradermal > subcutaneous > intramuscular > intravenous. However, there are several other injection types such intravitreal or intracaversonal that has a physiology of their own

Injection site: This important particularly for subcutaneous and intramuscular injections. Choosing the right area on your body for the injection will give the optimal physiological conditions for the injection, thickness of the subcutaneous tissue and underlying fat. However, it will also give you the best control of the injection which as a self-injecting patient could be very important to handle fear or discomfort.

The needle: Pushing a steel needle through skin is obviously an intrusion that could be painful. However, parameters such as needle thickness, tip cut or sharpness will greatly influence the perception of this intrusion. The needles used for injecting insulin today is around 0.25 mm thick whereas many monoclonal antibodies are injected with needles of 0.4 mm needle which is still quite thin. Also, the sharpness and cut of the needle tip has advanced considerably of the latest years introducing needles with multiple angles and shapes in the tip to reduce the impact in the injected tissue. Obviously, the choice of needle is dependent on the properties and volume of the solution to be injected. There are many products that could not be injected through a 0.25 mm needle within a reasonable time and without clogged needle etc.

Injection technique. How you hold the syringe when penetrating the skin and at what angle is obviously important to both optimize the physiology of the injection but also the perception. But the technical parameters starts before the actual injection. Pre-treating the injection site can be very important to improve the injection experience, both for children and adults. Simple procedures like pre-cooling the injection site with a cooler or applying a pain-reducing cream can be very efficient. There are now different stimulating devices which vibrates and distracts the injection in advance that can be quite efficient. Furthermore, typically many solution s for injections are refrigerated and warming or equilibrating the solution and syringe to room temperature before the injection is typically very useful to reduce any discomfort during the injection. In addition, the volume of injection is important, particularly for subcutaneous or intramuscular injections. Currently there is perceived barrier of <1 mL for sc or im injections. It is worth to keep in mind that this volume limitation is primarily driven by the fact that a self-injecting person cannot really be expected to sit and inject for more than 30-60 seconds which it takes to inject 1 mL. If you have a larger volume you could consider dividing up in two injections instead, which happens in reality.

Jonas Fransson

Dr Jonas Fransson is Director of Drug Product Development at Sobi AB, Stockholm, Sweden.

He is trained at Uppsala University and received a Ph.D in pharmaceutics in 1996. He has been working on protein product development, process development and packaging development since 1990. He has held various positions in the areas of design, formulation and manufacturing. He has worked in a number of development projects covering conventional injectables, ophthalmic delivery, injection devices and lyophilization development. Dr Fransson is responsible for formulations, packaging and device development. At Sobi he has developed a user-focused approach for product development. Jonas is also chairman of NextBioForm, an industry / academia collaboration in the design of user-centric biological products in Sweden.

> *"Simple [pretreatment] procedures like pre-cooling the injection site with a cooler or applying a pain-reducing cream can be very efficient."*

The Drug solution: Typically, and well justified drug formulations are designed to maintain the quality of the drug product as main objective. Obviously, the formulators are aware of the physiology of the body and try to as much as possible adjust to solution properties to be compatible with the tissues and fluids it will meet and mix with. Making the solution isotonic or at least reasonably hypertonic by adding a suitable tonicity agent (typically sodium chloride or mannitol) is key to avoid haemolysis. Formulating a physiological pH (i.e. 7.4) may be more challenging due to poor stability of your drug at this pH and "non-physiological" pH may be needed to target in the drug solution to have sufficient shelf life. However, using a low concentration of buffer may effectively reduce this issue as the body may neutralize the pH of the injected solution by its internal buffering system. Interestingly, with the introduction of many high concentration Monoclonal Antibodies and other protein therapeutics there has been findings that these high concentration protein solutions have a very good buffering capacity in their own and extra buffers may not even be needed. However, the buffered pH may still not be fully physiological. In addition, there are different stabilizing formulation components that may cause or reduce pain as well. It is a delicate task for the formulator to balance all these aspects when designing the product composition to have be injectable but have good stability at the same time.

In summary, "local tolerance" or perhaps "perception" of injections is an important aspect to carefully consider when designing products but also when designing treatment or procedure protocols. Although various types of injections have been used for more than 200 years there are still developments in this area. With the recent increase in use of biological therapeutics which are typically injected due to their high molecular weight this further emphasizes the needs for new technologies making the treatments acceptable and compliant ■

Jonas will be expanding on this topic at our 5th Annual Formulation & Drug Delivery Congress.

Hear his presentation '*Injection Pain Revisited; New Challenges With Biologicals*' on Day One in the stream '*Large Molecule Drug Formulation*'.

CONTINUOUS SOLID-STATE SYNTHESIS OF PHARMACEUTICAL COCRYSTALS AND SALTS

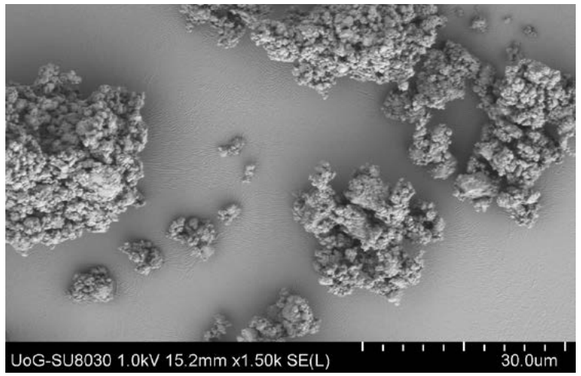
DR STEVEN ROSS AND PROF DENNIS DOUROUMIS

University of Greenwich, Faculty of Science and Engineering, Centre of Innovation and Process Engineering Research

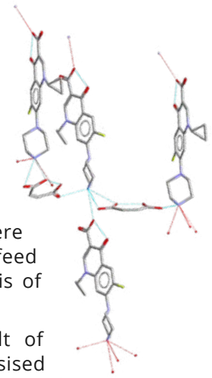
Multicomponent molecular assemblies such as cocrystals and salts provide exciting opportunities in the pharmaceutical industry for the development and manufacturing of new medicines. The development of such molecules results in the improvement of drug's poor physical properties substances such as processability, solubility, stability and bioavailability. The engineering of cocrystals and salts, focus on the formulation of thermodynamically stable crystalline forms with acceptable physical properties for a given compound. However, large-scale industrial exploitation of salification is limited, due to the limitations imposed by common manufacturing methods. One common problem plaguing the traditional manufacturing methods of salt production is that they require solvent addition to facilitate the process. Due to the ionic nature of salts, they have a propensity for solvate formation, leading to incomplete transformations and low-purity batches. In addition, conventional synthesis approaches are unsuitable for commercial manufacturing, as batch production methods provide limited scalability, low yields and additional solvent waste.

In recent years extrusion processing has been introduced as a continuous process for the synthesis of cocrystals/salts in solid state. The following are major advantages of this thermomechanical process:

- Complete formation of cocrystals/salts
- High purity (>99%)
- Continuous processing
- Solvent free process
- High throughput
- Coupling with process analytical tools

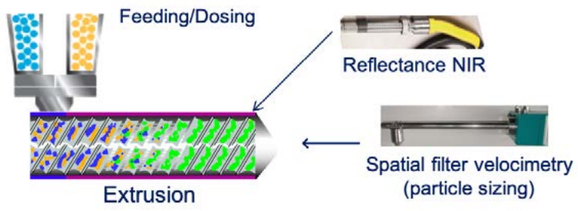


Our group has developed an engineering strategy for the selection of multicomponent systems which involves computational modelling for screening of drug – former pairs based on molecular complementarity and H-bond propensity screening. The selected pairs are ranked based on deviance from preferred parameters and likeliness to form H bonds. The pairs with the highest scores are forwarded for extrusion processing where the process is optimized (screw speed, feed rate, temperature profile) for the synthesis of high purity cocrystals/salts.



In a recent study, a pharmaceutical salt of ciprofloxacin – maleic acid was synthesised using twin screw extrusion processing, with liquid assisted grinding (LAG) used as a reference process. During extrusion, the drug – former pair was subjected to thermal and mechanical processing to form a salt though N+ - OH hydrogen bonding. By optimizing the temperature profile across the conveying/kneading zones and adjusting the screw configuration to allow for high-shear mixing, we were able to produce salts of excellent quality (100% match with reference structures) and increased dissolution rates over both the base components and LAG produced salts. X-ray and thermal analysis confirmed the salt purity with no unprocessed bulk materials and the presence of a single melting endotherm respectively. Previous studies have demonstrated that scale – up (>1.5Kg/h) of the synthesis is feasible and can be successfully done by defining the extrusion design space.

Thermomechanical extrusion processing is a superior manufacturing process for the development of multicomponent molecular assemblies and combined with molecular modelling significantly reduces experimental time and cost ■



LOW CONCENTRATION BIOPHARMACEUTICALS

SACHIN DUBEY

Sachin Dubey, PhD.
Head/Deputy Director of Formulation, Analytical and Drug Product Development
Glenmark Pharmaceuticals SA

Sachin Dubey is presently working with Glenmark Pharmaceuticals, Switzerland, where he is heading formulation, analytical and drug product development unit. His current responsibilities include designing and executing product development and characterization strategies for both early and late-stage products for Glenmark Biologics. Sachin earned his PhD from the University of Geneva, Switzerland and has previously worked with Novozymes Biopharma, Denmark. He has ~ 12 years of experience in biopharmaceutical formulation and analysis. Eleven formulations/presentations developed under his leadership are in different clinical trials. He has managed manufacturing of ~ 80 GMP batches of drug product/diluent/placebo spread across five different CMO's in USA/Europe. He is core member of various important teams within Glenmark, including CMC-regulatory strategies, process sciences leadership team etc. His principal research interests are protein formulation, stabilization, combinational product development, analytical characterization, DOE and QbD. He also has a keen interest in practicing lean principles. He has received multiple research awards and has several publications and presentations to his credit.

Biopharmaceuticals are target specific, large and complex molecules that are used as medicinal agents for the treatment of various diseases; the broad category is composed of different products with majority of them being recombinant proteins. Protein biopharmaceuticals are advancing and becoming more and more potent, leading to reduced dosing. Peptides and small proteins (insulin, interferon etc.) have been in market for over 3 decades, however most of these are used as sub cutaneous injection. Further development of monoclonal antibodies ex. bispecifics for oncology have led to the requirement of low concentration drug product development for i.v. infusion. This reduced dosing in addition to i.v. infusion requirement translates into low concentration drug product, which throws a variety of challenges at different stage of drug development.

The first challenge is from analytical perspective – most of the analytical methods for the release and characterization of bispecifics/antibodies are heavily influenced by concentration. More than 50% of these methods replies on detection by mean of UV signal either at 280 nm or at 214 nm. At low concentration UV absorbance is not sufficient to ensure reliable measurements and following two approaches are often helpful – 1) change of detector system to fluorescence and 2) pooling and concentrating multiple vials for analysis. Yet another challenge is the interference from excipients, at low protein concentration the ratio of excipient to protein is high and it's very important to ensure that the interference from excipient is properly studied during analytical method development. Furthermore for some of the bispecifics (depending on the format) quantification of impurities/variant in the form of homodimer can be extremely challenging, requiring mass spectrometry for analysis on a routine basis.

> *"Carefully designed formulation and process flow paths are important to ensure successful final product."*

Formulation and drug product development for low concentration is also challenging mainly by virtue of challenges arising from adsorption of protein to various different exposed surfaces as well as the additional stress a protein is exposed to, for example shear stress during pumping and filtration. Carefully designed formulation and process flow paths are important to ensure successful final product. Another challenge arises during manufacturing of low concentration biologics, especially when they are in lyophilized form. By virtue of their higher potency handling lyophilized form and evaluating potential vial breakage from safety perspective is important. Operator's exposure to the product during accidental vial breakage is a challenge as well as potential risk of cross contamination (if the facility is used for several products) and the measures to contain them could also require additional efforts.

The last and final part of a drug products journey is to be injected/infused in a patient and most of the protein therapeutics in oncology are infused after mixing them in commonly available saline/dextrose. During the infusion process the drug product (typical concentration is µg/mL) is diluted further and in addition this diluted drug product (typical concentration is ng/mL) is exposed to a series of different contact surfaces (by virtue of infusion bag, giving set lines, three way stop cocks, extension lines and needle/catheter). Additionally when the drug product is diluted it also lead to the dilution of its excipient which are responsible for product stabilization. Developing strategies to avoid any product loss and to ensure product stability upon dilution is extremely critical for this last step. Use of stabilizer have been shown to be a successful strategy for such preparation.

There is exciting time ahead of us with increasing potency of several biological therapeutics. More than 130 bispecifics are currently in clinical development in various phases; their approval will further foster research in this area. It is important to work very closely in interdisciplinary team of CMC, Clinicians and Pharmacist, right from the beginning of the project. Developing drug product while considering additional risks mentioned above will be helpful ■

CONTINUOUS MANUFACTURING OF PHARMACEUTICAL NANOCRYSTALS

LUIS PADRELA, KEVIN M RYAN, BARRY LONG

UNIVERSITY of LIMERICK
OLLSCOIL LUIMNIGH

Luis Padrela:
Lecturer in Bioprocess Engineering, Bernal Institute, University of Limerick

Kevin M Ryan: Chair in Chemical Nanotechnology, Bernal Institute, University of Limerick

Barry Long: PhD student working in the design of supercritical fluid methods for the continuous manufacture of pharmaceutical nanocrystals

Spray drying is a fast, continuous and single step process that is currently regarded as one of the most successful technologies used in the pharmaceutical industry for particle engineering of APIs (Active Pharmaceutical Ingredients). However, the solid-state nature of the spray-dried materials is often amorphous due to rapid solidification and is restricted to the micron size scale. Although amorphous materials provide huge improvements in the APIs apparent solubility, a major limitation of these materials is that the drug is thermodynamically unstable and tends to recrystallize during storage (depending on the stability provided by the polymer matrix in the solid dispersion) where the outcome might be a crystalline form with a much lower solubility.

Pharmaceutical crystalline materials provide a higher potential for enhanced solid state stability of poorly soluble APIs compared to amorphous materials, although providing poorer solubilities and dissolution rates. Interestingly, producing crystalline APIs as nanoparticles provides considerable improvements in their solubility, dissolution rate as well as solid-state stability. One of the most successful top-down methods used to produce APIs nanocrystals with the desired size distribution consists of wet milling APIs down to a nano sized range, adding excipients/surfactants to these nanosuspensions to inhibit crystal growth due to Ostwald ripening and spray drying them later on. However, milling limits the control of the API crystal habit and other surface properties, can take long times to achieve the required size and it might not provide sufficiently small sizes for different types of APIs.

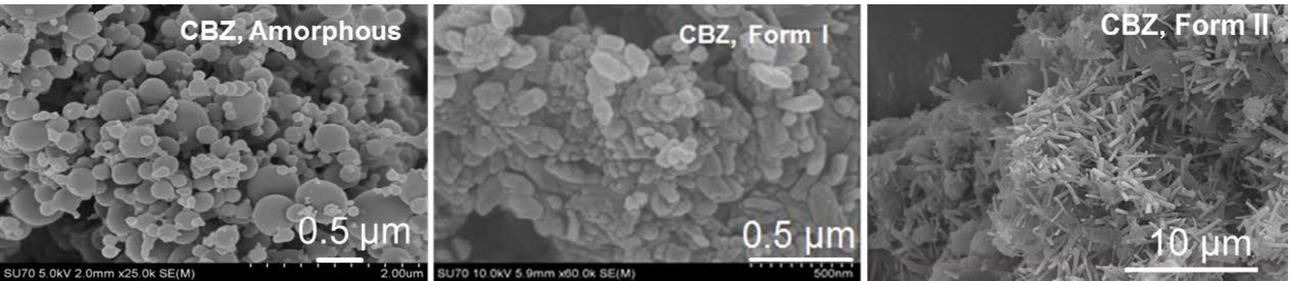
In this study, a supercritical CO2-assisted spray drying method was used to produce and control the solid-state form/polymorphic form of Carbamazepine (CBZ) nanoparticles. This process involves contacting the API solution (carbamazepine dissolved in methanol) with supercritical CO2 in the nozzle and immediately spraying it through the nozzle exit for solvent extraction at atmospheric pressure. By restricting the high pressure exclusively to where it is indispensable, it is possible to control the precipitation of the API before the nozzle (anti-solvent nucleation/crystallization) or after the nozzle (atomization/spray drying) while providing processing flexibility. This also facilitates the adaptation of this technology onto existing spray drying equipments.

Our team is currently finalizing the optimization of novel isolation mechanisms for the drug nanoparticles produced after supercritical assisted spray drying. These isolation methods provide high yields for the collection of nanoparticles in a format that enables their downstream processing. Key features of this continuous manufacturing technology include:

- Controlled production of nanoparticles (100-5000 nm) in one single step
- Efficient isolation of nanoparticles with optimal rheological properties
- Increases yield and stability of nanoparticles leading to improved process capability and product control
- Telescopes across multiple steps reducing the total number of unit operations and decreasing manufacturing footprint
- Is drop-in technology, integrateable with current process operations

Luis will be expanding on this topic at our 5th Annual Formulation & Drug Delivery Congress as part of our Formulation & Delivery Series UK.

Hear his presentation '*Supercritical CO2-Assisted Spray Drying For The Generation Of Tailored API Nanoparticles*' on Day Two at 16:00.



INTRATUMOURAL CONTROLLED RELEASE DRUG DEPOTS FOR FOCAL CANCER TREATMENT

STEFAN GRUDÉN, MOUSTAPHA HASSAN, NIKLAS AXÉN

NanoZolid® is an injectable and bioresorbable biomaterial for focal controlled release drug delivery without the need for post-treatment surgical implant removal. This study concerns an injectable, two-component drug formulation based on calcium sulfate that solidifies in vivo to form a solid local depot (NanoZolid®). Due to an optimisation of the microstructure using high pressure (isostatic pressure during re-crystallization) of one component of the biomaterial, the drug release rate can be controlled (Fig. 1). Injectable depot formulations based on biomaterials for long-term drug release have numerous applications for local and focal treatment of cancers while reducing systemic side-effects, e.g. for anti-cancer drug substances such as cytostatics, immuno-active agents and hormones.

The department of Laboratory Medicine, Experimental Cancer Medicine, at Karolinska Institutet in Huddinge, Sweden, conducts world-leading research in cancer medicine. One major goal is to improve the survival rate and quality of life for cancer patients treated with cytostatics and stem cell transplantation through increased treatment efficacy and decreased or eliminated side effects.

By combining the know-how related to the NanoZolid® technology with the well-reputed research at Karolinska Institutet, the project interweaves the expertise of three different areas of science: the sciences of biomaterials; dosage form design; and, dedicated cancer research.

Stefan Grudén will describe the project, the technology and its potential for cancer treatments, at the 5th Annual Formulation & Drug Delivery Congress. The scanning electron microscopy image below shows the microstructure of the depot (Fig. 2) ■

STEFAN GRUDÉN
Head of Pharmaceutical Research & Development
Lidds Pharma

Stefan Grudén holds a position as Director of Pharmaceutical R&D at the Uppsala-based Swedish pharmaceutical company LIDDS and is also a PhD student at Karolinska Institutet, Stockholm. He has worked in the science field of dosage form design and development and held senior positions for 20+ years and has been an invited speaker at the Swedish Pharmaceutical Society on the conference Optimizing Drug Delivery to the Target and on the Nordic Innovative Drug Delivery Meeting. He has recently published two papers; one describing the NanoZolid® technology, and one preclinical study investigating intra-tumoral injections in mice.

Moustapha Hassan: Professor at the Dept. of Lab. Medicine, Karolinska Institutet, Huddinge, Sweden

Niklas Axén: Associate Professor and inventor of the NanoZolid® technology, LIDDS AB, Sweden

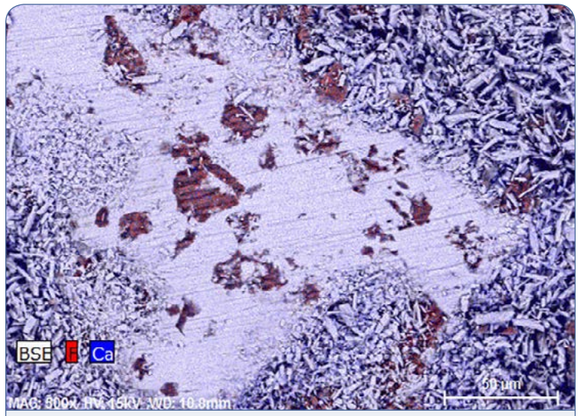


Fig. 2: Scanning electron microscopy (SEM) with energy dispersive X-ray analysis (EDX) mapping image of microstructure of NanoZolid® in solidified form, showing precipitates of 2-hydroxy-flutamide (red) in the porous matrix as well as in the densified granules (white-grey).

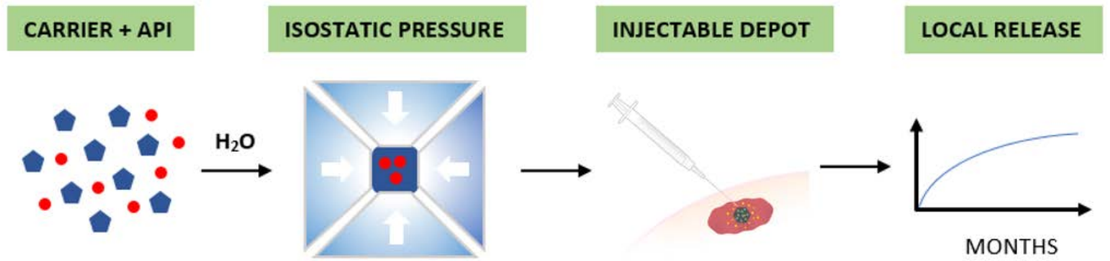
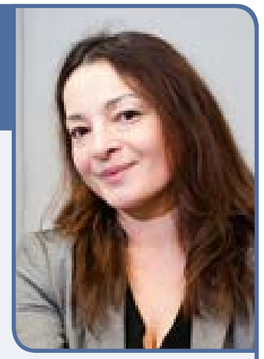


Fig. 1: Schematic illustration of the NanoZolid® technology

NANOPARTICLES FOR FOCUSED ULTRASOUND DRUG DELIVERY

MAYA THANOU



Maya Thanou,
Reader,
King's College London

Maya Thanou is Reader in the Institute of Pharmaceutical Science, King's College London. Prior to that she was a Dorothy Hodgkin Royal Society Research Fellow at Imperial College London, at the Department of Chemistry and the Genetic Therapies Centre, in the area of cancer genetic therapies. In her current post she is focusing her research in the area of Chemical Biology and Drug Delivery. Dr Thanou has achieved research funding over £2M during the last years. She has supervised 10 PhD students she is the author of 80 peer reviewed papers and chapters (h-index 30). She is the editor of the RSC book Theranostics and image guided drug delivery. Her project has been selected by King's Commercialisation Institute as one of the best 6 project in the Institute. She is the key inventor of 8 patents all in the area of formulation and drug delivery. She is the co-founder of AJMMed-i-caps a start-up developing combination technologies (microelectronics and nanotechnology) for colorectal cancer early detection.

The development of nanoparticles for therapeutic applications was first described in 1959 by the Nobelist Richard Feynman in his famous lecture "there is plenty of room at the bottom". Since then, the emerged field of nanomedicine has been gaining more attention for a number of therapeutic applications with the development of cancer treatment as priority. A more recent trend has been the development of stimuli responsive particles, many of these have been formulated to be responsive to; pH, enzymes, redox, (internal triggers) temperature and pressure (external triggers). In particular, the development and application of temperature and pressure sensitive particles activated by focused ultrasound is an emerging field for efficient drug delivery. Nanoparticles that can be used in conjunction with ultrasound for drug delivery include: 1) thermosensitive liposomes, 2) theranostic liposomes, 3) nanobubbles 4) nanodroplets.

High intensity focused ultrasound (HIFU) is a method which enables the deposition of energy within a lesion without damaging the surrounding healthy tissue. High intensity focused ultrasound devices are mainly extracorporeal systems that target areas in the body as deep as 10 cm from the skin. Focusing of ultrasound beams can be achieved novel devices such as multi-element phased array transducer that adjust to a focal point electronically. High intensity focused ultrasound energy generates heat at a focal point of up to 85 °C. On the other hand MRI is used to monitor the temperature increases, via MR thermometry. Being able to monitor the temperature is essential to spatiotemporally control of the energy deposition. This lead to the development of magnetic resonance guided focused ultrasound (MRgFUS). The technique uses MR images to generate precise anatomical images of the tumour, that can then be used as a guide for the ultrasound treatment controlled by the temperature feedback. This non-invasive technique uses an MRI temperature map to continuously measure temperature changes inside the body, pinpointing and guiding the treatment. This is a new, FDA-approved, treatment for lesions and in research trials to improve drugs' both distribution and permeation through membranes.

Image Guided Drug delivery refers to the combination of drug targeting, imaging and intervention. Image-guided drug delivery can be used for several different purposes, e.g. for improving biodistribution, bioavailability, target site accumulation, drug release and drug efficacy. Clinically, it holds significant potential for cancer treatments. Image-guided drug delivery has the potential to facilitate and advance personalised nanomedicine treatments.

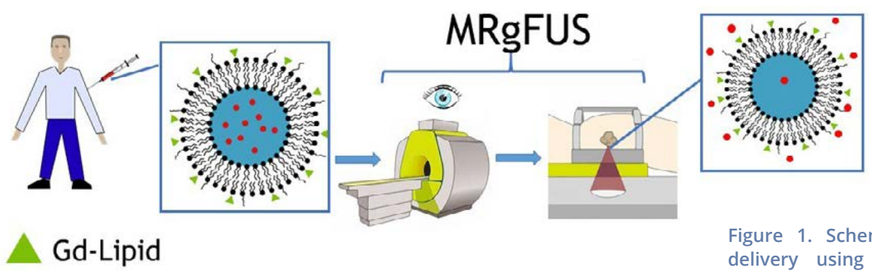


Figure 1. Schematic of image guide drug delivery using thermosensitive liposomes labelled for MR imaging and MRgFUS

We suggest the combination of labelled thermo-responsive nanoparticles and MRgFUS as an efficient method to substantially improve tumour drug availability (Figure 1).

Nanoparticles accumulate in tumours initially through the enhanced permeation and retention effect (EPR). MR imaging locates the nanoparticles (through Gadolinium contrast agents coupled onto the membrane) and coordinates with the focused ultrasound to provide the energy to increase the temperature locally at 42°C. Increase of the temperature in a control manner has a dual effect. On one hand temperature rise increases the permeability of the blood vessels, which allows more nanoparticles to enter the tumour (Super-EPR) , on the other hand it induces a rapid drug release through the phase change thermo-responsive liposomes.

Figure 2 show this effect in mice administered nanoparticles labelled with imaging lipids and carrying the drug topotecan that has an intrinsic fluorescence. Topotecan's fluorescence is quenched in the nanoparticle but recovers immediately when released. In this mouse the tumour on the right is treated with short applications of Focused Ultrasound. This leads to increased nanoparticle accumulation compared to the left tumour and a simultaneous drug release from the nanoparticles due to thermosensitivity.

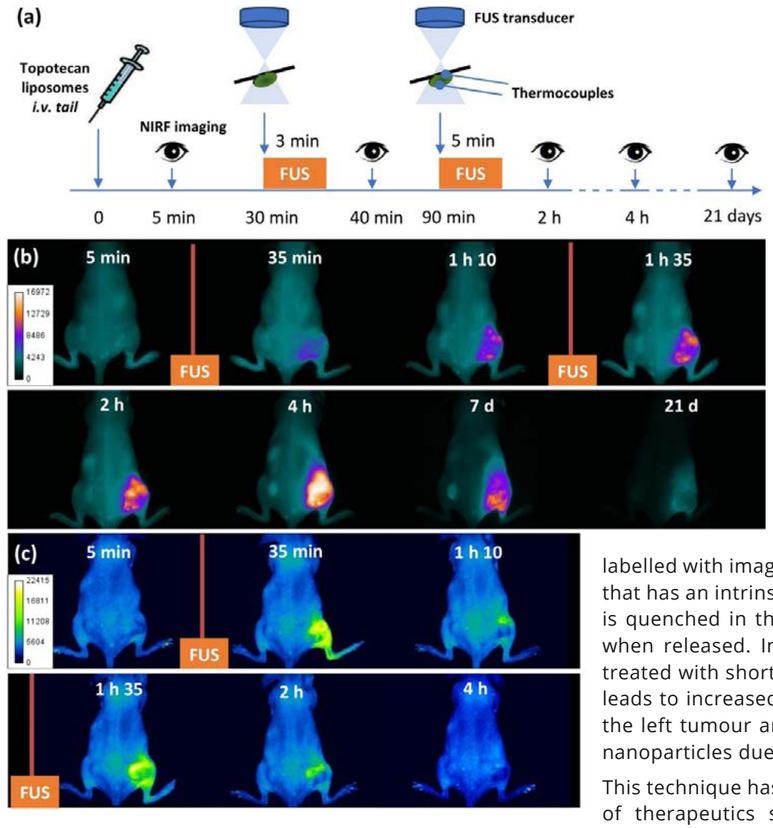


Fig. 2a) Schematic of hyperthermia treatment regime.

Fig. 2b) Near infrared fluorescence imaging of labelled nanoparticles from tumour uptake after treatment (label on the lipid).

Fig. 2c) Intrinsic topotecan fluorescence images indicating drug release from the liposomes after application of Focused Ultrasound. Centelles et al. Journal of Controlled Release, 2018.

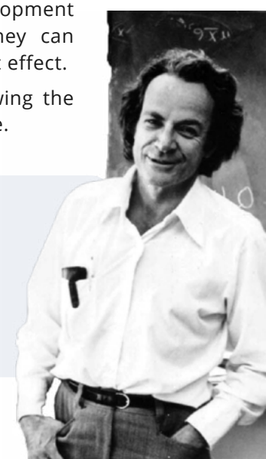
This technique has been applied successfully with a number of therapeutics such as antibodies (and derivatives), a number of small molecule drugs, and nucleic acids such as siRNA. In all cases focused ultrasound improves the drug's tumour biodistribution.

Currently combinations of focused ultrasound and drug therapies are in clinical trials for a number of indications. The technique holds promise for efficient drug delivery in brain and pancreatic tumours where the surrounding tissue forms a barrier for drugs to reach their target.

Imaging can be combined with other interventions for accurate drug delivery as long as the drug is labelled. A number of technologies are in development that when combined with drugs they can significantly increase their therapeutic effect.

Richard Feynman's vision of "swallowing the surgeon" does not appear impossible.

Maya will be speaking at our 5th Annual Formulation & Drug Delivery Congress, with her presentation '*Imaging siRNA Complexes In Vivo*' on Day One in the stream '*Delivery For Rna Therapies*'.



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Senior Director, Formulation Development
Shire


RICCARDO TOROSANTUCCI
Head, Formulation Development, Biologics
Sanofi


JONAS FRANSSON
Director
Swedish Orphan Biovitrum


JUHO JALKANEN
Chief Development Officer
Faron Pharmaceuticals


PARESH VADGAMA
Principal Scientist
Glenmark Pharmaceuticals


JONAS FAST
Senior Scientist, Early-Stage Pharmaceutical Development & GLP Supplies
F. Hoffmann La-Roche


ROBERT MUELLER
Principal Scientist, Late-Stage Pharmaceutical & Processing Development
F. Hoffmann La-Roche Ltd.


PAUL DALBY
Professor
University College London

STREAM 2 ADVANCES IN DRUG DELIVERY


VINCENT LING
Senior Director, Materials and Innovation, Drug Product Development,
Takeda

THERESA SCHEUBLE
Director, Research & Development
Janssen


CORINNA SONDEREGGER
Head of Portfolio Management, Device Development & Commercialisation
Novartis


AKTHAM ABURUB
Senior Research Advisor, Pharmaceutical Product Design
Eli Lilly & Company


ALEXANDER SCHEER
Chief Scientific Officer
EryTech

YING WANG
Senior Principal Scientist
Pfizer


KOMEI OKABE
Senior Researcher, Advanced Technology
Santen

STREAM 3 CONTINUOUS MANUFACTURING & PROCESSING / DELIVERY FOR RNA THERAPIES


EKKEHARD LEBERER
Senior Director, R&D Alliance Management
Sanofi


SHALINI ANDERSSON
Senior Director, Head of New Therapeutic Modalities
AstraZeneca


AHMED YOUSSEF
Head of Manufacturing Science & Technology, Parenterals
Bayer


SACHIN DUBEY
Head of Formulation & Analytical Development
Glenmark Pharmaceuticals


HEINRICH HAAS
Vice President, RNA Formulation & Drug Delivery
BioNTech


CEDRIC GYSEL
Healthcare Solutions Design Manager, **Johnson & Johnson**


ANTONIO BENEDETTI
Chemometrician & Engineer, Manufacturing Simulation & Modelling
GlaxoSmithKline


DENNIS DOUROUMIS
Professor in Pharmaceutical Technology and Process Engineering
University of Greenwich

MAYA THANOU
Senior Reader
King's College London

STREAM 4 DEVELOPMENT & FORMULATION OF INHALED THERAPIES


TARIQ SETHI
Vice President Translational Medicine Unit Early Clinical Development
AstraZeneca


RICHARD KAYE
Director, CMC Leader For Respiratory
GlaxoSmithKline


ERICA BÄCKSTRÖM
Associate Principal Scientist
AstraZeneca


GEORGINA MARSH
Senior Formulation Scientist In Oral Formulation
AstraZeneca


ROBERT IVES
Investigator & Associate Fellow
GlaxoSmithKline


DANIELA RICCARDI
Professor, Deputy Head
University of Cardiff


ADNAN CUSTOVIC
Clinical Professor of Paediatric Allergy
Imperial College London


STRAVROS KASSINOS
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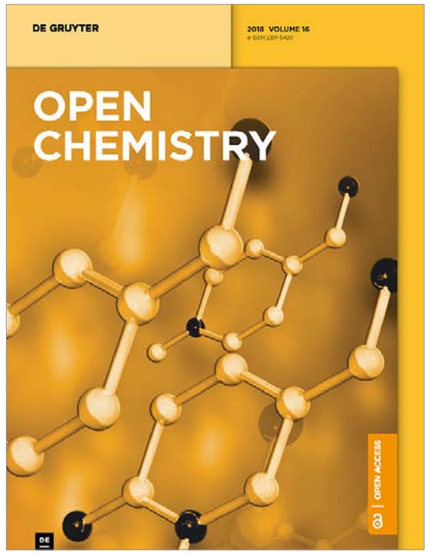

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