



PDDS 2017

Global Conference on

**Pharmaceuticals *and*
Drug Delivery Systems**

JUNE 29 TO JULY 01
2017

Venue

Eurostars Rey Don Jaime
Av. de les Balears, 2, 46023
Valencia, Spain

PDDS 2017

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Welcome Message



Dear Attendees, Presenters, Organizing Committee and Distinguished Guests,

On behalf of the organizers, we would like to cordially invite you to participate in the 'Global Conference on Pharmaceutics and Drug Delivery Systems' during June 29 - July 1 at Valencia, Spain.

Mark your calendars for one of world's leading Pharmacy conferences (PDDS 2017) which will be a unique Academy program to build communities of common interest in cutting-edge sciences. It is an assemblage of scientists and research professionals in the field of Pharmaceutics and Drug Delivery systems, where you will have a great opportunity to share ideas and knowledge as well as collaborate/network with other scientists.

Discussing on various imperative topics will add an insight to ponder and discuss over today's scientific and technological challenges. PDDS 2017 is an excellent scientific forum to unveil the novel developments and to reflect on ideas and realities by discussing practical experiences.

Thank you for your continued support. We look forward to seeing you in Valencia, Spain!

Dr. Teruna J. Siahaan

*Aya & Takeru Higuchi Distinguished Professor
Department of Pharmaceutical Chemistry
The University of Kansas
USA*

Professor Ulla Langel

*Dpt. Neurochemistry
Stockholm University
Sweden*

PDDS 2017

Welcome Message

Dear Attendees, Presenters, Organizing Committee and Distinguished Guests,



On behalf of Magnus Group and conference organizing committee, we would like to cordially invite you to participate in the 'Global Conference on Pharmaceutics and Drug Delivery Systems (PDDS 2017). The conference takes place Thursday June 29 to Saturday July 1, 2017 at Eurostars Rey Don Jaime in Valencia, Spain.

The Pharma Conference Europe is designed to assist fellow researchers by reviewing current practice and policies while disseminating examples of successful innovation. Our PDDS

2017 conference is an opportunity for top researchers, experts and thinkers in academia, industry, and government from around the world to exchange ideas on a number of critical topics in the field of pharmaceutics and drug delivery systems. It is a unique chance to meet research professionals to collaborate on research projects or to build institutional capacity in implementing and designing effective higher education policies. The conference offers unparalleled professional and educational development opportunities for fellow researchers.

We look forward to seeing you in Valencia, Spain!

Professor Esmail Jabbari

*Chemical Engineering, Biomedical Engineering
College of Engineering and Computing
University of South Carolina
USA*

PDDS 2017

Keynote Speakers



Gus R. Rosania
University of Michigan
College of Pharmacy, USA



Esmail Jabbari
University of South Carolina
USA



Ulo Langel
Stockholm University
Sweden



Ernst Wagner
Ludwig-Maximilians-Universi-
tat Munich and Nanosystems
Initiative Munich, Germany



Teruna J. Siahaan
University of Kansas
USA



Arwyn T. Jones
Cardiff University
UK



Carmen Popescu
Roquette America
USA



El Hassane Larhrib
University of Huddersfield
UK



Mino R. Caira
University of Cape Town
South Africa



Ricardo Perez Tomas
University of Barcelona
Spain



Gillian Hutcheon
Liverpool John Moores
University, UK



Mehmet Ay
CanakkaleOnsekiz Mart
University, Turkey



Ana Carolina Kogawa
UnivEstadualPaulista - UNESP
Brazil

About Magnus Group



Magnus Group (MG) is initiated to meet a need or to pursue collective goals of scientific community, especially in exchanging the ideas which facilitates growth of research and development. We specialize in organizing conferences, meetings and workshops internationally to overcome the problem of good and direct communication between scientists, researchers working in same fields or in interdisciplinary research.

MG promotes open discussions and free exchange of ideas at the research frontiers mainly focusing on science field. Intense discussions and examination based on professional interests will be an added advantage for the scientists and helps them learn most advance aspects of their field.

It proves that these events provide a way for valuable means of disseminating information and ideas that cannot be achieved by usual channels of communications. To encourage an informal community atmosphere usually we select conference venues which are chosen partly for their scenic and often isolated nature. Suggestion from many scientists and their reviews on our conferences reflected us to continue organizing annual conferences globally.

About PDDS 2017

PDDS 2017 is designed to assist fellow researchers by reviewing current practice and policies while disseminating examples of successful innovation. The Pharma Conferences Europe is a unique chance to meet different leaders and experts in your field, to share experiences & perspectives and to build institutional capacity in implementing and designing effective higher education policies.

Our expert honorary speakers will provide you with the most clinically up-to-date relevant information, you'll leave better educated and more invigorated than you thought possible.



PDDS 2017

DAY 1

Keynote Forum

Global Conference on
**Pharmaceuticals and
Drug Delivery Systems**

June 29 - July 01, 2017 | Valencia, Spain

PDDS 2017

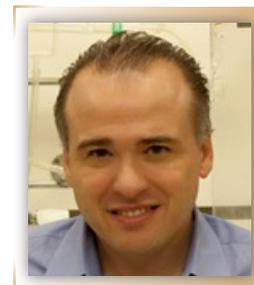
Pharmaceutics and Drug Delivery Systems

June 29 - July 01, 2017
Valencia, Spain

Macrophage-stabilized drug crystals

Gus R. Rosania *Ph.D*

University of Michigan College of Pharmacy, USA



Poorly soluble drugs with slow rates of clearance are poised to precipitate in the organism following long term oral administration. In this context, my research group has been characterizing the intracellular crystal-like drug inclusions (CLDIs) that are formed by clofazimine, an antimycobacterial drug that is FDA-approved for the treatment of leprosy, and part of the WHO list of essential medications. Using mice as a model organism to study CLDI formation, we have employed X-ray diffraction and other physical methods to elucidate the molecular structure of CLDIs down to the atomic level. In addition, we have biochemically isolated CLDIs from the spleen and livers of drug-treated mice, and have studied the biological effects of CLDIs in relation to soluble clofazimine *in vitro* and *in vivo*, demonstrating that CLD possess potent anti-inflammatory activity. Using synthetic formulations of clofazimine that are designed to resemble CLDIs, we are exploring how biomimetic formulations of macrophage-stabilized drug crystals can be exploited as macrophage targeted, locally active, anti-inflammatory agents.

Takeaway Notes

- New pharmacokinetic phenomena (insoluble drug complexes).
- New tools for studying drug transport from the whole organism down to molecular and atomic level.
- New, revolutionary approach to formulation and drug delivery.

Biography

Gus R. Rosania, PhD is Professor of Pharmaceutical Sciences at the University of Michigan where he has been Principal Investigator of an NIH funded, internationally-recognized research group for the past fifteen years. At the forefront of pharmacokinetics research, his lab has performed pioneering research on the transport mechanisms governing the distribution of poorly soluble small molecule drugs, from cells to whole organisms. He has published over sixty original research articles and is inventor on six patents. He is a member of the editorial board of various pharmaceutical sciences journals and has received numerous awards for his scientific contributions at the interface of chemistry, biology and pharmaceutics.

Pharmaceutics and Drug Delivery Systems

June 29 - July 01, 2017
Valencia, Spain

Engineered spatiotemporal delivery of morphogens for skeletal regeneration

Esmaiel Jabbari *Ph.D*

University of South Carolina, USA



Osteogenesis and vascularization during bone development are coupled by spatiotemporal regulation of paracrine signaling in which the invading vascular endothelial cells secrete osteogenic morphogens to stimulate cell differentiation and bone formation. Conversely, the differentiating mesenchymal stem cells (MSCs) in the vicinity of the vascular endothelial cells release vasculogenic morphogens to further stimulate vasculogenesis for the metabolically highly active osteoblasts. I will demonstrate in the first part of the presentation that timed and localized release of bone morphogenetic protein-2 (BMP2) and vascular endothelial growth factor-165 (VEGF) morphogens using nanogels in a micro-patterned co-culture system synergistically enhances the expression of paracrine signaling factors, such as bFGF, and couples osteogenesis to vasculogenesis. Articular cartilage is a multifunctional tissue with a highly organized structure which provides a lubricating surface for the gliding joint and a load bearing matrix attached to the underlying bone. During fetal cartilage tissue development, changes in biochemical, mechanical, and geometrical factors direct the formation of stratified structure of articular cartilage. I will demonstrate in the second part of the presentation that spatial gradients in multiple morphogens recreates the zonal organization of articular cartilage.

Acknowledgements: This work was supported by research grants from the US National Science Foundation under grant Nos. DMR1049381, IIP-1357109, and CBET1403545, the US National Institutes of Health under grant No. AR063745, and the Arbeitsgemeinschaft Fur Osteosynthesefragen (AO) Foundation under grant No. C10-44J.

Takeaway Notes

- New technologies for growth factor delivery
- Challenges in protein delivery
- Nanoparticle delivery systems
- Cell delivery by encapsulation in hydrogels

Biography

Esmaiel Jabbari completed his PhD at Purdue University and postdoctoral studies at Monsanto, Rice University, and Mayo Clinic. He is Director of Tissue Engineering and Drug Delivery Laboratory and Full Professor of Chemical and Biomedical Engineering at University of South Carolina. He received the Berton Rahn Award from AO Foundation in 2012 and the Stephen Milam Award from Oral and Maxillofacial Surgery Foundation in 2008. He was elected to the College of Fellows of AIMBE in 2013. He has published >230 peer-reviewed articles and >260 seminars. He serves as Academic Editor of PLOS ONE.

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Transfection by cell-penetrating peptides

Ülo Langel

Stockholm University, Sweden



Recent data on mechanisms and applications of transfection strategies by cell penetrating peptides (CPP) are summarized on the variety of different oligonucleotide cargoes including plasmid, antisense and siRNA oligonucleotides. Introduction of PepFect and NickFect technologies for oligonucleotide transfection by transportan-based cell-penetrating peptides in vitro and in vivo is described. 403. Kurrikoff, K., Gestin, M., and Langel, Ü. (2016) Recent in vivo advances in cell-penetrating peptide-assisted drug delivery. *Expert Opinion on Drug Delivery*, 13(3), 373-387.

Takeaway Notes

- CPP technology for ON transfection, efficient ON transfection in vitro and in vivo, mechanisms of CPP transfection.

Biography

Ülo Langel is a Professor at the Department of Neurochemistry, Stockholm University, and at the Institute of Technology, Tartu University. Prof. Langel has been selected as a Fellow Member of International Neuropeptide Society (1995), and is a member of Academia Europaea. He is a coauthor of more than 400 scientific articles and 20 approved patents or patent applications.

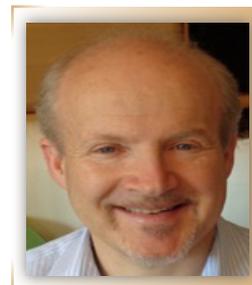
Pharmaceutics and Drug Delivery Systems

June 29 - July 01, 2017
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Bioinspired sequence-defined drug, protein and gene carriers by chemical evolution

Ernst Wagner *Prof, PhD*

Ludwig-Maximilians-Universität Munich and Nanosystems Initiative Munich, Germany



Viruses and protein toxins present natural examples for potent intracellular delivery of nucleic acids or proteins. Natural evolution has optimized such carriers that comprise multiple different functions for overcoming the delivery barriers. The evolution process takes advantage of the definition of each carrier as a specific amino acid sequence stored in form of a genetic sequence. Refinement of sequences occurred by local variations such as mutations, deletions, additions, or larger rearrangements such as domain shuffling, followed by functional selection for a biological task in the set environment. We intend to use these basic design principles of natural evolution for the generation of artificial drug delivery systems. A chemical evolution process may take advantage of combining empirical with rational design and utilize a far more diverse chemical design space than the natural variation of only 20 amino acids.

Chemical evolution includes identification of chemical motifs for specific delivery steps and assembly of such micro-domains into defined larger sequences. It includes rational or random variation and rearrangement into various topologies, followed by screening for a pre-defined delivery task. Chemical motifs may include but are not restricted to natural amino acid sequences. For example, polymer units like polyethylene glycol or PEI, despite their simple structure, can exert delivery functions such as shielding or endosomal escape, respectively, with similar efficacy as far more complex natural proteins. In search for improved carriers, we focus on the assembly of building blocks into libraries of defined oligoaminoamide sequences by semi-manual or automated solid phase-assisted synthesis. Formulation with the intended cargo (drug, protein, pDNA, siRNA) are screened in relevant biological models.

Takeaway Notes

- Innovative therapeutic agents like genes, intracellular nanobodies or siRNA need intracellular delivery
- Sequence-defined assembly combines multifunctional carrier design with pharmaceutical precision
- Bioinspired chemical evolution enables optimization of drug carriers
- Tumor-targeted siRNA or gene delivery in vivo demonstrated in pharmacological murine models

Biography

Dr. Wagner is full professor of Pharmaceutical Biotechnology at LMU since 2001 and member of the Munich Center for Nanoscience. He coordinates 'Biomedical Nanotechnologies' of the Excellence Cluster NIM. After a PhD from TU Vienna and postdoc at ETH Zürich, he was Group Leader at the IMP Vienna (1987-1995) and Director for Cancer Vaccines at BoehringerIngelheim Austria (1992-2001). Dr. Wagner has authored >403 publications (h-index 72). He is Board member of the German Society for Gene Therapy, Committee member of ASGCT, and BSA member of CRS. He is Editor of Pharmaceutical Research and Editor-in-Chief of The Journal of Gene Medicine.

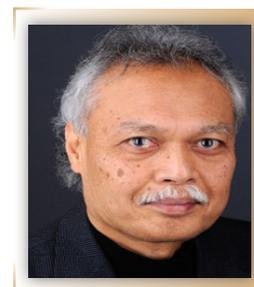
Pharmaceutics and Drug Delivery Systems

June 29 - July 01, 2017
Valencia, Spain

Challenge and progress in delivering molecules to the brain

Teruna J. Siahaan

University of Kansas, USA



One of the major challenges in studying brain function and diseases (i.e., Alzheimer's, Parkinson's, multiple sclerosis (MS), and brain tumors) lies in the difficulty in delivering molecules to the brain. The critical obstacle *in vivo* is the presence of the blood-brain barrier (BBB). In addition, a very large portion (98%) of currently available drugs to treat diseases cannot be used to treat brain diseases. The long-term goal is to develop novel methods to analyze the chemical, cellular, and extracellular components of the brain to determine their functions in normal and brain-diseased animals. The short-term goal of this project is to deliver peptides and proteins with imaging labels that can be used to detect changes in the brains of animal models of brain diseases such as Alzheimer's, MS, and brain tumors. The central hypothesis is that modulating cadherin-mediated cell-cell adhesion in the BBB using HAV and ADT peptides can enhance the paracellular permeation of small-to-large molecules through the BBB. The results showed that cadherin peptides (i.e., HAV- and ADT-peptides) increase the *in vivo* brain delivery of drugs (camptothecin), paracellular marker molecules (^{14}C -mannitol, gadopentetic acid (Gd-DTPA), ^3H -PEG, and 25 kDa IRdye800cw-PEG), efflux pump substrates (rhodamine 800 (R800), ^3H -daunomycin), 8–12 amino acid peptides (i.e., cIBR7 and cLABL), and proteins (i.e., 65 kDa Gd-DTPA-albumin (galbumin)) in mice and rats. These results strongly support the possibility of using cadherin peptides for non-invasive delivery of various molecules for diagnostic or therapeutic purposes to the brains of animal models of brain diseases. The HAV and ADT peptides are non-toxic, and they can safely modulate the BBB for a short period to allow BBB penetration of large proteins. Using NMR spectroscopy and molecular modeling, we also found that ADT and HAV peptides bind to the EC1 domain of E-cadherin at different binding sites. In summary, our work is the first to show that modulating cell-cell adhesion can safely increase the delivery of molecules to the brain in living mice and rats. The concept of modulating cell-cell adhesion of the BBB to improve delivery of molecules to the brain is novel and would have a broad impact on the diagnosis and treatment of brain diseases.

Biography

Professor Teruna Siahaan earned a B.S. and an M.S. from the University of Indonesia and a Ph.D. from the University of Arizona. He completed a postdoctoral fellowship at the University of California, Santa Barbara. His research interests are in the utilization and modulation of cell adhesion molecules on the cell surface for targeted drug delivery to a specific cell type and for enhancing drug permeation through the intestinal mucosa and blood-brain barrier (BBB). Dr. Siahaan's group is using E-cadherin peptides to enhance permeation of large hydrophilic molecules (i.e., peptides and proteins) through the intestinal mucosa and BBB. The hypothesis is that E-cadherin peptides modulate the E-cadherin interactions at the intercellular junctions to create larger openings that will allow paracellular permeation of large hydrophilic molecules (e.g., peptides and proteins). His group is also using peptides derived from cell adhesion molecules (i.e., ICAM-1 and LFA-1) to target drugs to leukocytes and vascular endothelial cells in inflammatory and autoimmune diseases (i.e., rheumatoid arthritis). Cell adhesion peptides are being used to target antigenic peptides (i.e., bi-functional peptide inhibitor (BPI)) to block the formation of the immunological synapse at the interface between T cells and antigen presenting cells (APC). BPI molecules have been shown to suppress autoimmune disease models such as multiple sclerosis, type-1 diabetes and rheumatoid arthritis.

DAY 1

Speakers

Global Conference on
**Pharmaceuticals and
Drug Delivery Systems**

June 29 - July 01, 2017 | Valencia, Spain

PDDS 2017

Session on: Novel Developments In Drug Delivery System | Advanced Drug Delivery Systems

Session Chairs

Ernst Wagner

Ludwig-Maximilians-Universität Munich and
Nanosystems Initiative Munich, Germany

Teruna J. Siahaan

University of Kansas, USA

Session Introduction

Title: Targeted self-navigating multifunctional drug delivery vehicles driven by promiscuous landscape phage proteins

Valery A. Petrenko, Auburn University, USA

Title: Nucleic acid based amphiphiles as soft materials for nanomedicine

Philippe Barthelemy, University of Bordeaux, France

Title: Patient centric drug delivery systems: ODT (Oral Disintegrating Tablet) and ODF (Oral Disintegrating Film)

Carmen Popescu, Roquette America, USA

Title: Formulation of liposomal doxorubicin modified with Bombesin peptide for selective targeting of GRP receptors over-expressed by cancer cells

Giancarlo Morelli, University of Naples Federico II, Italy

Title: Development of receptor targeted nanocomplexes for delivery of RNA therapeutics to the lung

Stephen Hart, UCL GOS Institute of Child Health, UK

Title: Drug delivery across the skin barrier using biocompatible thermoresponsive nanogels

Fiorenza Rancan, Charite - Universitätsmedizin Berlin, Germany

Title: Engineering endosomal escape using pHlexi particles

Georgina Kate Such, The University of Melbourne, Australia

Title: Aptamers as therapeutic agents in human cancers and evidence for glioblastoma targeting through the blood-brain-barrier of aptamer-functionalized nanosystems

Laura Cerchia, Istituto per l'Endocrinologia e l'Oncologia Sperimentale "G. Salvatore" (IEOS), Italy

Title: Building a better antibody-based medicine: Antibody mimetic

Hanieh Khalili, University of East London, UK

Title: Oral delivery of lipophilic drugs: The solubility-permeability interplay and formulation design

Arik Dahan, Ben-Gurion University of the Negev, Israel

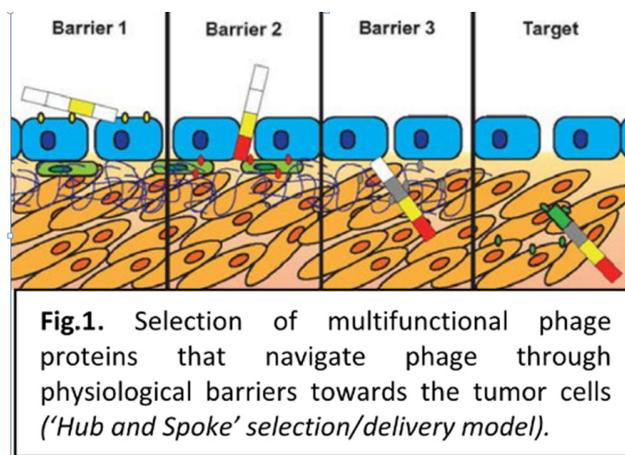
Title: Inhalable therapy of pulmonary Tuberculosis mediated by polysaccharide microparticles

Ana Margarida Grenha, University of Algarve, Portugal

Targeted self-navigating multifunctional drug delivery vehicles driven by promiscuous landscape phage proteins

Valery A. Petrenko, Ph.D., D.Sci.* & James W. Gillespie, Ph.D
 Auburn University, USA

Development of precision medicines acting specifically at the site of disease has been a long sought goal for the last century, starting from pioneering works of Paul Ehrlich, who suggested the concept of site-directed chemotherapeutics or ‘magic bullet’. With the development of nanomedicines, significant progress towards this goal have been reached. In particular, active targeting has been proposed to enhance the therapeutic efficacy of nanomedicines. Unfolding the complexity of the tumor microenvironment has revealed additional biological barriers hindering efficacy of the targeted drug delivery. To overcome specific barriers, it was suggested to supply the tumor-targeting ligands with a combination of multiple ligands with appropriate functions. This trend in using ‘molecular cocktails’ will likely prevail as a necessity for success of actively targeted nanomedicines. To prove this new concept, we developed several actively targeted nanomedicine systems that explore ~500 fusion phage proteins in various specifically designed molecular selection schemes that are based on the desired outcome, for example, ability to bind cancer cellular receptors, penetrate into the cells, accommodate at specific cellular compartments, and ultimately—produce expected cytotoxic effect of the phage protein-targeted nanomedicines. We observed, however, that not all nanomedicine-linked phage protein specifically interacting with cancer cells can induce inhibition of tumor growth in vivo. These and other controversial results discussed recently in the literature, forced us to modify the traditional concept of drug targeting and suggest a novel paradigm called ‘drug navigation’. We used our proprietary polyvalent phage displayed ‘landscape’ peptide libraries to select clones with specificity to various cancer types, which resulted in generating phage protein fusions containing functional motifs with selectivity to various cellular phenotypes and discovery of ‘promiscuous’ multi-motif phage proteins targeted to different cellular receptors. Studying homology of hundreds thousands of binding phage-displayed peptides, we identified short linear motifs containing 3-4 amino acid residues, which accumulate in the displayed peptides during different rounds of selection. We hypothesized that these motifs serving as the elementary binding units in the processes of phage-involved molecular recognition would provide the solid theoretical basis for rational design of molecular probes for studying and control of various biological systems, including tumor microenvironment. Discovery of short motifs serving as elementary binding units during phage selection inspired us to propose the novel “addressed drug navigation” concept, which relies on the use of “molecular self-navigating ligands”, selected from tissue-migrating polyvalent multi-motif landscape phage display libraries and accumulating ‘elementary binding units’ responsible for binding to different tissue cells, as illustrated in the Fig.1. This novel approach promises to replace the existing ‘point to point’ targeting concept for the novel ‘self-navigating’ drug delivery paradigm that can be used as a theoretical basis in development of a novel generation of molecular imaging probes and medications for precise and personal medicine.



Pharmaceutics and Drug Delivery Systems

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Takeaway Notes

- How to use polyvalent phage-display libraries and other phage toolkits for development of targeted self-navigating multifunctional drug delivery vehicles;
- How to develop tissue-migrating multi-motif landscape phage probes by micro-biopanning in vivo of polyvalent landscape phage displayed libraries;
- How to use the databases of multifunctional peptides and elementary binding units in a rational design of self-navigating drug delivery systems in accordance with 'Hub and Spoke' delivery mode.;
- How to use polyvalent phage-display libraries in other areas of bioengineering (epitope discovery, vaccine development, molecular imaging, etc.)

Biography

Valery A. Petrenko, Professor at Auburn University; graduated from Moscow State University, U.S.S.R (1972); received PhD and D.Sc. degrees in chemistry from the Institute of Organic Chemistry (1976) and Moscow State University, U.S.S.R (1988), Honor Ranks of Senior Scientist in Bioorganic Chemistry (1984) and Professor in Molecular Biology (1992) from the Government of the U.S.S.R. In 1977 he moved to Novosibirsk and worked as Junior and Senior Scientist (1977-1982), Laboratory Head (1982-1985), Associate Director for Research (1985-1989), Director of Institute, Vice President for Research and Professor (1989-1993) in Scientific Association Vector (Novosibirsk, Russia). In 1993 he joined the faculty of University of Missouri-Columbia as Visiting Professor and Research Professor, and in 2000 - Auburn University as Professor (2001). Dr. Petrenko pioneered polyvalent phage display technology and established research programs focused on development of diagnostic and therapeutic probes using phage display and phage nanobiotechnology. He is a Member of National Academy of Inventors Chapter (2013), Auburn University Research Initiative in Cancer (AURIC), National Cancer Institute (NCI) Alliance for Nanotechnology in Cancer (2009) and Phi Zeta Honor Society of Veterinary Medicine.

Nucleic acid based amphiphiles as soft materials for nanomedicine

Philippe Barthélémy
University of Bordeaux, France

The combination of nucleic acids chemistry (e.g., nucleoside, nucleotides, oligonucleotides) with supramolecular principles provides an efficient and powerful approach to prepare well-defined systems with tunable physico-chemical properties and functions. We develop new nano-systems based on nucleic acids chemistry for i) drug delivery applications (therapeutic, theranostic), and ii) tissue engineering. This communication will present novel “smart” nucleic acid derivatives (nucleolipids, Glycosylated-nucleolipidsetc) developed in our lab.

Takeaway Notes

- Lipid based drug delivery systems
- Hydrogels for sustained drug release and regenerative medicine
- Nucleic acid chemistry and biology

Biography

Philippe Barthélémy received his doctorate in chemistry from the University of Montpellier II, France in 1993. He was then a postdoctoral fellow at Emory University in the group of Pr Fredric Menger (Lavoisier Grant and Emory Fellowship). In 1995 he was appointed as a temporary lecturer at the University of Avignon and as Associate Professor at the same University in 1996. P. Barthélémy worked also as a Visiting Associate Professor at Duke University in 2001. In 2005 he was appointed as full Professor at the University of Bordeaux Segalen. He is leading the “ChemBioPharm” team of the INSERM U1212. Philippe Barthélémy was Vice President of the University of Bordeaux Segalen (2011-2013). Over the course of his tenure, Barthelemy’s research has yielded more than 110 peer-reviewed publications, more than 15 patents and patent applications, and more than 100 oral invited conferences and oral presentations.

Patient centric drug delivery systems: ODT (Oral Disintegrating Tablet) and ODF (Oral Disintegrating Film)

Carmen Popescu Ph.D
Roquette America, USA

Fast disintegration formulations like Oral Disintegrating Tablets (ODT) and Oral Disintegration Films (ODF) were emerging in the last decade due to the fact they offer patient convenience and compliance by fast dissolving or disintegrate in the mouth while in contact with the available 2ml saliva by delivering the actives directly to systemic circulation through buccal mucosa. Both ODT and ODF are suited for drugs, which undergo high first pass metabolism by improving their bioavailability and reducing dose frequency, which in turn is minimizing adverse/side effects. They are cost effective, easy to scale up, possess good stability, accurate dosing and easy handling by patients on the go. In addition, they are patient centric (pediatrics, geriatrics, psychiatric patients with dysphagia) drug delivery systems design to increase patient compliance. ODT/ODF are preferred to classic dosage forms (swallowble/ chewable/ suckable tablets) due to ease of administration (portability, “on the go”) without water, pleasant taste and mouth feel more of “a treat” than a treatment. Manufacturer’s attraction for these dosage forms resides in improved life cycle management, market differentiation, innovation and brand creation. Moreover, in recent years we can see their remarkable expansion from Rx to OTC, nutraceuticals (vitamins, minerals, etc.) and biologics. In response to the increased popularity of ODT on the market the excipients industry created ready to use platforms in order to ease formulation process. The presentation is focusing on: definition of ODT and ODF, benefits and disadvantages of fast dissolving formulations, how to select the best formulation composition and process in order to accommodate physical and chemical API’s properties, commercially available products and how can they be suitable for both small /large molecule delivery. Recently FDA approved an ODT formulation using 3D printing and a lot of research work is focusing on ODF by 2D printing as a step forward to personalized drug delivery systems.

Takeaway Notes:

- Describe the advantages and disadvantages of ODT and ODF as solid dosage form delivery
- Identify the excipients and processes associated with fast dissolving delivery systems formulation and the suitable APIs
- Summarize the need for fast disintegrating systems and their flexibility in formulation and process scaling up

Biography

Dr. Carmen Popescu got her B.S. degree in Physics and Ph.D. in Biophysics at University of Bucharest, Romania. She is a Senior Project Coordinator at Roquette America Inc., located in Geneva, Illinois. She came to USA in 1999, as an Associate Professor with University of Illinois at Chicago, College of Pharmacy where she is still an Adjunct Associate Professor. In her career, she focused on the development of classic dosage forms (liquid, semi-solid and solid dosage forms formulation) as well as drug delivery systems (microparticles, nanoparticles, liposomes, niozome) for small and large molecules. She has published over 120 research papers, book chapters and presentations. You can find her publications on: https://www.researchgate.net/profile/Carmen_Popescu3

She is also an Adjunct Associate Professor with Roosevelt University and University of Tennessee. She is teaching in “Tablets & Capsules Hands-on Short Course” at Univ. of Maryland and “Hands-on Tablet Technology Course” at Univ. of Mississippi.

Formulation of liposomal doxorubicin modified with Bombesin peptide for selective targeting of GRP Receptors over-expressed by cancer cells

Antonella Accardo¹, Ph.D.; Elena Nicolato², Ph.D.; Silvia Mannucci², Ph.D.; Pasquina Marzola², Ph.D.; and Federica Vurro²; Giancarlo Morelli^{1*}

¹Dept. of Pharmacy, University of Naples Federico II, Napoli, Italy

²University of Verona, Italy

The presentation concerns the obtainment of liposomal doxorubicin in which liposomes are externally modified with a targeting peptide able to drive liposomal doxorubicin in a selective way on membrane receptors over expressed in tumours. We have developed a kit containing a first vial filled with a sterile, translucent, red dispersion of the liposomal doxorubicin drug; a second vial filled with a modified phospholipid with a reactive function such as DSPE-Peg-maleimide in lyophilized form; and a third vial filled with a peptide modified with an appropriate reactive function, in a 1:1 stoichiometric amount respect to compound 1 and in lyophilized form. The chosen peptide is a stable analogue of 1-9 Bombesin peptide; it is very stable in serum, maintains high specificity, with nanomolar affinity, toward GRP receptors over-expressed by cancer cells, and it acts as a bombesin antagonist, thus it does not interfere with biological pathways promoted by the bombesin peptide. Its efficacy in selective targeting of GRP receptors has been efficiently demonstrated in vitro and in vivo by nuclear medicine experiments, also when the peptide sequence is modified, as happens in peptide-liposome preparations, on its N-terminus. Results of animal studies concerning the in vivo use of liposomal doxorubicin modified with the targeting bombesin peptide will be presented; they clearly indicate that in mice treated with the kit product (i.e. Doxil modified with the Bombesin analog) tumor growth is absent and in some cases tumor regression is observed, with an improved efficacy respect to mice treated with non-modified Doxil or with non-liposomal Doxorubicin.

Takeaway Notes:

- The audience will benefit of new efficient methods for preparation of liposomal drugs modified with targeting agents such as peptides and antibodies.
- We will provide practical solutions to overcome technologic problems for the preparation of specific liposomal drugs ready to use in clinical studies and in human therapy.
- Moreover the audience will know the importance of targeting peptide receptors in different human tumors with more emphasis on the over-expression of bombesin receptors in different malignancies such as prostate, ovarian and breast cancers.

Biography

Giancarlo Morelli is full professor of Chemistry at Dept. of Pharmacy University of Naples "Federico II". He is Director of a Research Center on Bioactive Peptides (CIRPeB) and President of the Italian Society of Peptides (ItPS). His research interest is in peptide chemistry; his researches are focused on different aspects of peptide science, particularly he studied application of new designed peptides for selective targeting of contrast agents for MRI or Nuclear Medicine and for drugs and liposomal drugs. Giancarlo Morelli is also Chairman of the International Workshops on Bioactive peptides organized in Naples every two years and now at the 15th edition. G. Morelli is author of more than 150 papers most of them concerning the development of Peptide Science.

Development of receptor targeted nanocomplexes for delivery of RNA therapeutics to the lung

Aristides D Tagalakis¹ PhD, Ahmad M Aldossary¹ MSc, Melis Dalbay¹ PhD, Dania Grant-Serroukh¹, Ileana Guerrini¹ PhD, Mustafa M Munye¹ PhD, Glaxo SmithKline¹, Amy Walker¹ MSc, Francesca Drew¹ BSc, Mayuran Mathiyalakan¹ BSc, Rositsa Ivanova¹ PhD, Hanpeng Chen² BSc, Claire M Smith¹ PhD, Stuart A Jones², Guy WJ Moss¹ PhD, Robin J McAulity¹ PhD & Stephen L Hart^{1*}

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Cystic Fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene (CFTR), encoding a cyclic AMP-activated chloride channel. CFTR deficiency also regulates the epithelial sodium channel, ENaC, leading to increased sodium and water absorption from the overlying airway surface liquid leading to thickened mucus and impaired mucociliary clearance allowing bacterial infections to become established that contribute to the CF lung pathology. We are investigating novel nucleic acid based therapies for CF including inhibition of ENaC by RNA inhibition (RNAi), and correction of the CFTR protein deficiency by mRNA therapy or gene editing. Delivery of nucleic acids to the lung is particularly challenging and so our aims were; 1) to develop and optimise targeted RNA containing nanocomplexes for penetration of mucus and epithelial cell transfection; 2) evaluate molecular and functional effects of nucleic acid therapeutics in air-liquid interface (ALI) cell culture models of the human airway epithelium and; 3) assess translational potential by transfection of mice lungs.

We are developing nanocomplexes (called RTNs) that are optimized for lung transfection. RTNs comprise formulations of liposomes and epithelial receptor-targeting peptides which self-assemble on mixing with siRNA or mRNA although the optimal composition varies with the type of RNA. The biophysical properties and transfection efficiency of RTNs were unaltered by nebulisation offering a convenient route for delivery. Modifying the surface properties of the nanocomplexes altered their diffusion properties in mucus with anionic surface charge or PEGylation of cationic formulations providing enhanced mobility in mucus. Thus, the surface properties of the RTNs appear to facilitate transit through mucus.

ENaC silencing levels of 30% were achieved with RTN siRNA nanocomplexes in human CF cells grown in ALI cultures which was sufficient to correct the electrical properties of the epithelium and led to rehydration of the mucus and fluids above the epithelium and restoration of normal cilia beating frequency (CBF). In vivo, transfections in normal mice showed single doses of siRNA delivered by oropharyngeal instillation in mouse lung silenced α ENaC by ~30%, while three doses of siRNA delivered at 48 h intervals resulted in ~60% silencing, similar to ALI transfection data. Silencing persisted for at least 7 days and all the mice tolerated well the dosing with RTNs as shown histologically suggesting benefits of persistence and safety. RTNs containing mRNA encoding luciferase displayed expression levels more than 200-fold higher than with plasmid DNA and with much lower levels of inflammation.

The RTNs with siRNA and mRNA described here are compatible with airway delivery and possess properties that enable them to overcome mucociliary barriers leading to efficient silencing of ENaC or expression of proteins encoded by mRNA in vitro and in vivo. ENaC silencing restored epithelial hydration and ciliary function. These results support the hypothesis of RNA based therapies for CF and demonstrate a method of delivery.

Takeaway Notes:

- Design of nanoparticles for penetration of mucus
- Design of nanoparticles for packaging and delivery of siRNA and mRNA.
- Functional correction assays in cell culture for cystic fibrosis

Biography

Stephen Hart is Professor in Molecular Genetics at UCL GOS Institute of Child Health. After receiving his PhD from the University of Cape Town in Microbial Genetics in 1991, he worked as a postdoc at St Marys Hospital Medical School, London working on gene therapy for cystic fibrosis before joining the Institute of Child Health in 1994 where his research has continued in developing gene therapies with nanotechnologies for neuroblastoma, cardiovascular disease, primary ciliary dyskinesia and genetic disease of the skin, as well as cystic fibrosis. He is the author of almost 100 peer reviewed papers as well as five current patents in nanotechnologies. In 2011, he founded a spin-out company, Nanogenic Solutions, to develop therapeutics based on these patented technologies.

Drug delivery across the skin barrier using biocompatible thermoresponsive nanogels

Fiorenza Rancan^{1*} Ph.D., Jana Jurisch¹ B.Sc., Michael Giubudagian² M.Sc., Marcelo Calderón² Ph.D., Ulrike Blume-Peytavi¹ M.D., and Annika Vogt¹ M.D.

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Several new therapeutic agents for the treatment of dermatological conditions are emerging. Despite skin accessibility, delivery of drugs across skin and maintenance of a sufficient drug concentration in the target region needs further improvement. Nanocarrier-based approaches are promising strategies for the further development of dermal and transdermal drug delivery. Different types of nanocarriers possess different physicochemical characteristics and have different penetration and drug release properties upon interaction with skin barriers and cell components. A systematic correlation between nanocarrier physicochemical characteristics and their behavior after topical application is necessary to foster the use of nanotechnology in dermatology. Methods like electron microscopy, atomic force microscopy, stimulated Raman spectroscopy and flow cytometry of single cell suspensions were utilized to determine nanocarriers physicochemical properties and their performance after application on human skin explants. Softness, stability and stimuli-responsiveness have been identified as the most promising characteristics influencing nanocarrier penetration and drug delivery to skin. In particular, soft thermoresponsive nanogels were found to penetrate deeply within the stratum corneum, the outermost skin barrier, changing its permeability and improving drug penetration. Interaction of nanogels with skin antigen presenting cells occurred in both epidermis and dermis. These findings suggest the possibility to develop targeting approaches in order to increase drug delivery to specific cell populations.

Takeaway Notes:

- The importance to correlate chemical composition and physical properties to nanocarrier behavior and delivery performance after topical application on skin will be stressed.
- The talk will illustrate how nanocarriers intrinsic properties can be used to improve skin permeability.
- Methods to monitor the interaction of nanocarriers with skin immune system will be shown.

Biography

Fiorenza Rancan is senior scientist at the Clinical Research Center for Hair and Skin Science at the Charité University of Berlin, Germany. Her expertise lays on nanocarriers penetration and drug delivery in human skin using ex-vivo and skin organ culture models. Her main research topics are the use of biodegradable particles (e.g. PLA and virus-like particles) for the delivery of adjuvants and antigens to skin (transcutaneous vaccination), the exploration of soft thermoresponsive nanocarriers for the treatment of skin inflammatory conditions giving special attention to antigen presenting cells, and the development of new antimicrobial treatments using skin models for infected chronic wounds.

Engineering endosomal escape using pHlexi particles

Nachnicha Kongkatigumjorn¹ (MSc), Christina Cortez-Jugo² (PhD), Ewa Czuba² (BSc), Adelene Sue Mei Wong^{1,2} (BEng), Rebecca Yvonne Hodgetts¹ (MSc), Angus Philip Rayner Johnston² (PhD), and Georgina Kate Such^{1*} (PhD)

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The design of ‘smart’ delivery systems with tunable response to their environment is important for developing new therapies, as they allow efficient and controlled therapeutic release to a specific target site. Self-assembled polymeric carriers have generated significant interest for such applications due to their simple and versatile synthesis. However, such carriers are still limited by inefficient delivery to target regions within the cell, therefore central to improving the efficacy of such carriers is the ability to control their cellular trafficking. A key bottleneck in cellular delivery is escape of the polymeric carrier from acidic, cellular compartments (lysosomes/endosomes) into the cytoplasm, referred to as endosomal escape. These compartments have lower pH than the blood stream thus this pH variation can be used to induce carrier disassembly and release of functional cargo. PH responsive materials have also shown potential for endosomal escape. One interesting pH responsive polymer is poly(2-(diethylamino)ethyl methacrylate) (PDEAEMA) as it undergoes a transition from hydrophobic to hydrophilic within a relevant pH range. In this presentation new pH responsive PDEAEMA (pHlexi) particles will be reported and their properties engineered to tune endosomal escape properties.

PDEAEMA particles (pHlexi particles) are interesting model delivery systems as they are simple and modular with rapid pH disassembly. Our work has demonstrated these particles undergo endosomal escape and these escape properties can be tuned by the molecular weight of the polymer building blocks, with a decrease in escape when the polymer Mn was decreased. In addition, the disassembly pH of the pHlexi particles could be tuned by adding additional monomers. It was found disassembly pH showed a direct relationship with endosomal escape percentage, it decreased from 90% to 0% as the pH of disassembly decreased. The responsive and modular nature of these materials provides new insights into the design of nanoengineered materials for application in drug and gene delivery.

Takeaway Notes:

- Explain the challenges of engineering endosomal escape of polymer carriers.
- Demonstrate the simple and versatile synthesis of pH responsive nanoparticles.
- Show how endosomal escape can be engineered by changing molecular weight of carrier.
- Show how endosomal escape can be engineered by changing composition of polymer building blocks.

This talk provides important insights into how particle engineering can play a significant role in cellular trafficking, factors that should be considered for applications that require delivery of biological therapeutics.

Biography

Dr Georgina Such completed her PhD in 2006 from the University of New South Wales. After her PhD, Dr Such commenced postdoctoral work in the Nanostructured Interfaces and Materials Science (NIMS) group headed by Professor Frank Caruso. Her research in this group focused on making nanoscale polymer carriers for targeted drug delivery. In 2013, she commenced a Future Fellowship in the School of Chemistry, The University of Melbourne, enabling her to start her own research group in the area of ‘smart’ materials. Dr Such is now a senior lecturer at the University of Melbourne. Dr Such has authored 65 peer-reviewed publications including 3 book chapters. Her work has been recognized with the 2011 L’Oreal Women in Science Fellowship. Her research interests include polymer synthesis, self-assembly and ‘smart’ materials.

Aptamers as therapeutic agents in human cancers and evidence for glioblastoma targeting through the blood-brain-barrier of aptamer-functionalized nanosystems.

¹Simona Camorani, Ph.D.; ¹Elvira Crescenzi, Ph.D.; ¹Monica Fedele, Ph.D.; ²Mario Chiariello, Ph.D.; ³Mauro Comes Franchini, Ph.D.; ⁴Antonella Zannetti, Ph.D. and ^{1*}Laura Cerchia, Ph.D.

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Highly selective compounds emerging for anti-cancer therapy are oligonucleotide aptamers that interact with their targets by recognizing a specific three-dimensional structure. Thanks to their unique properties (small size, high selectivity and sensitivity, high stability, convenient synthesis and modification, lack of immunogenicity), aptamers have been proved as a valid alternative to antibodies as targeted cancer therapeutic agents on their own or as carriers of chemotherapeutic agents, small interfering RNAs or drug-loaded nanoparticles. Although the SELEX (Systematic Evolution of Ligands by Exponential enrichment) process to isolate aptamers is typically carried out using purified target molecules, we employ whole live cells as selection targets in order to obtain aptamers against cell surface proteins in their native conformation and even in the absence of prior knowledge of biomarkers present at the cell surface. Here, we report our recent data on the tumor targeting properties and preclinical evaluation of two validated aptamers, that we previously generated by cell-SELEX as high specific ligands of epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor β (PDGFR β). Their therapeutic effects have been investigated in human glioblastoma (GBM) and triple negative breast cancers (TNBCs), heterogeneous cancers still lacking of targeted therapeutic options. Moreover, the results obtained so far on the selection of novel TNBC-specific aptamers, will be discussed as well.

Polymeric nanoparticles (PNPs) offer unique possibility for in vivo delivery of diagnostics and/or therapeutics to tumor tissues, when conjugated to specific targeting agents. We will describe the preparation of drug-loaded PNPs conjugated with the anti-PDGFR β aptamer which, in vitro, are able of high uptake into GBM cells and kill them when loaded with a PI3K-mTOR inhibitor. Ultimately, in vivo, we also demonstrate the blood-brain-barrier passage and tumor accumulation in an orthotopic model of human GBM.

Takeaway Notes:

The audience will know our research approach from the generation of oligonucleotide aptamers to their development as tools to: 1) identify novel biomarkers for human cancers; 2) discriminate different subtypes of heterogeneous human cancers; 3) interfere with malignant phenotype on their own and/or in combination with conventional chemotherapy; 4) deliver drug-loaded nanoparticles specifically to target cancer cells. The proposed research has the potential to lead a revolution in the development of anti-cancer drugs and should inspire other attempts to harness aptamer technology for improved cancer treatment.

Biography

Laura Cerchia is Staff Scientist and Group Leader at Istituto per l'Endocrinologia e l'Oncologia Sperimentale "G. Salvatore", Consiglio Nazionale delle Ricerche (CNR-IEOS) since 2008. After she received her PhD from the University of Naples "Federico II" in Biochemical Sciences in 1997, she worked as CNR fixed-term researcher focusing on the development by the SELEX technology of aptamers specific for new tumor associated antigens and their preclinical evaluation as anti-cancer agents. Since 2007, she is Principal Investigator of research projects granted by Worldwide Cancer Research and AIRC. She is inventor of four patents on the cell-SELEX and the individual generated aptamers.

Building a better antibody-based medicine: Antibody mimetic

Hanieh Khalili*, P. T. Khaw, S. Brocchini
University of East London, UK

Therapeutic proteins (e.g. monoclonal antibodies, cytokines, and enzymes) are widely used in healthcare. Monoclonal antibodies (particularly IgGs) are an important class of protein based-medicine which tend to aggregate and misfold. Therefore, development of stable IgGs remains one of the key challenges in biotechnology. To extend the utility of IgGs much research is focused to stabilize IgGs as highly concentrated solutions, which can be self-administered by patients. We have developed a novel antibody mimetic which has comparable binding characteristic to IgGs, but appeared to be much less prone to aggregation. IgG antibodies are bivalent molecules with two Fabs (antigen binding fragment) and a fragment crystallisable (Fc). To generate antibody mimetic which is called Fab-PEG-Fab (FpF), two Fabs are conjugated together with poly (ethylene glycol) PEG at a site near where they are bound to the hinge in an IgG (Fig 1). PEG acts as a flexible scaffold between the two Fabs to mimic the natural flexibility of the Fabs in an IgG.

A case study of FpF prepared from infliximab, to act as a better antibody-based mimetic for ocular indication will be discussed in this talk. Infliximab is an antibody IgG1 that neutralizes TNF- α and is used off label by systemic administration to treat ocular inflammatory diseases such as uveitis. We prepared the Fab-PEG-Fab (FpF_{infliximab}) from infliximab for direct intravitreal injection. FpF_{infliximab} was designed to address side effects caused by antibody degradation and the presence of the Fc. Biacore analysis indicated that infliximab and FpF_{infliximab} maintained binding affinity for both human and murine recombinant TNF- α , while slower dissociation rate constant observed for FpF_{infliximab}. No Fc mediated RPE cellular uptake was observed for FpF_{infliximab}. Both infliximab and FpF_{infliximab} suppressed inflammation by reducing the number of CD45+ infiltrate cells in the EAU mice model after a single intravitreal injection at the onset of peak disease. Infliximab and FpF_{infliximab} are equally effective to modulate the acute inflammatory response that characterizes EAU. These results offer an opportunity to develop and formulate FpF molecules designed for single and potentially multiple targets using bi-specific FpFs.

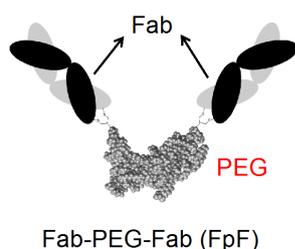


Fig 1. Structure of antibody mimetic

Takeaway Notes:

- Learn about different formats of antibody-based medicine
- Learn on antibody mimetics and the reason for their development
- Learn on bispecific format for antibody-based medicine
- Learn on application of biologics for ocular indication such as ocular inflammation

Biography

Hanieh Khalili is a lecturer in Pharmaceutical science at University of East London (UEL) School of Health, Sport and Bioscience. Before moving on to a lectureship, she did a postdoctoral research associate at University College of London (UCL) School of Pharmacy and Institute of Ophthalmology working on development, and formulation of antibody mimetics for ocular inflammation. She completed her PhD in antibody modification and formulation in the Pharmaceuticals Department at UCL School of Pharmacy. Previously she earned a MSc with distinction in Drug Delivery from UCL School of Pharmacy. She have also received a BSc in chemistry and MSc in Analytical Chemistry. Her research focus is on development and formulation of bispecific antibodies and fusion proteins to modulate ocular healing after surgery and to develop dosage forms to inhibit inflammation, angiogenesis and fibrosis generally within the eye.

Oral delivery of lipophilic drugs: The solubility-permeability interplay and formulation design

Prof. Arik Dahan, Ph.D

Ben-Gurion University of the Negev, Beer-Sheva, Israel

Poor aqueous solubility is a major challenge in today's biopharmaceutics. While solubility-enabling formulations can significantly increase the apparent solubility of the drug, the concomitant effect on the drug's apparent permeability has been largely overlooked. The mathematical equation to describe the membrane permeability of a drug comprises the membrane/aqueous partition coefficient, which in turn is dependent on the drug's apparent solubility in the GI milieu, suggesting that the solubility and the permeability are closely related, exhibit a certain interplay between them, and treating the one irrespectively of the other may be insufficient. In this lecture, an overview of this solubility-permeability interplay will be provided, and the available data will be analyzed in the context of the effort to maximize the overall drug exposure. Overall, depending on the type of solubility-permeability interplay, the permeability may decrease, remain unchanged, and even increase, in a way that may critically affect the formulation capability to improve the overall absorption. Therefore, an intelligent design of solubility-enabling formulation needs to consider both the solubility afforded by the formulation and the permeability in the new luminal environment resulting from the formulation.

Takeaway Notes:

Overall, depending on the type of solubility-permeability interplay, the permeability may decrease, remain unchanged, and even increase, in a way that may critically affect the formulation capability to improve the overall absorption; the audience will learn that intelligent design of solubility-enabling formulation needs to consider both the solubility afforded by the formulation and the permeability in the new luminal environment resulting from the formulation. The audience will be able to implement these principles to develop better oral formulations for lipophilic drug candidates.

Biography

Arik Dahan is an Associate Professor of Pharmaceutics and Biopharmaceutics at the Department of Clinical Pharmacology and the School of Pharmacy, Ben-Gurion University of the Negev in Beer-Sheva, Israel. He is also an Adjunct Professor of Pharmaceutical Sciences at the College of Pharmacy, University of Michigan, USA. Dr Dahan received his Ph.D. (2007) from the Hebrew University of Jerusalem. From 2007 until 2009 he was a Post-Doctoral Research Fellow at the University of Michigan College of Pharmacy with Professor Gordon Amidon. Dr Dahan's research interest is the integration of up-to-date molecular and cellular mechanistic investigations of drug disposition in the context of the human body, in order to enable successful drug delivery and therapy. In implementing this molecular biopharmaceutical approach to ADME research, Dr Dahan is seeking to enable mechanistic-based successful solutions to drug delivery, especially (but not only) oral, in challenging scenarios e.g. low-solubility, low-permeability, efflux transport, extensive metabolism, poor site targeting, various pathophysiological conditions (e.g. obesity, inflammatory bowel disease), and pediatrics patient care. He has authored over 70 top-notch Journal papers, and contributed chapters to 7 books.

Inhalable therapy of pulmonary tuberculosis mediated by polysaccharide microparticles

Ana Grenha*, PhD; Ludmylla Cunha, MSc; Susana Rodrigues, MSc; Flavia Musacchio, MSc, Filipa Guerreiro, MSc
University of Algarve, Portugal

Tuberculosis remains a leading cause of death, although effective therapy is available for many years. Therapeutic failure is mainly due to non-compliance with prolonged treatments, often associated with severe side-effects. New therapeutic strategies are therefore demanded. As tuberculosis is an air-borne pathology and the lung is the primary site of infection, with alveolar macrophages hosting mycobacteria, direct lung delivery of antibiotics appears as a potentially effective approach. In this context, therapeutic success depends on suitable carriers that reach the alveolar zone and on their ability to undergo macrophage capture, providing the intracellular accumulation of drugs.

This work proposes alternative inhalable tuberculosis therapy based on spray-dried polysaccharide-based microparticles. Several polysaccharides have been tested, including locust bean gum, chondroitin sulfate, fucoidan, chitosan, xanthan gum, among others. Isoniazid and rifabutin, two first-line antitubercular drugs, were simultaneously associated to microparticles in order to establish a combined therapy, as recommended by WHO. The proposed polysaccharides bear structural units (mannose, fucose and galactose units, sulfate groups, etc.) that may provide privileged targeting of macrophage surface receptors. The aerodynamic properties of microparticles were characterized, as well as their ability to provide specific macrophage targeting. The cytotoxic effect of microparticles in cells relevant for the objective of the work (A549 alveolar epithelial cells, macrophage-derived THP-1 cells) was determined. Considering that most of the proposed polysaccharides have not been explored for pulmonary delivery, an *in vivo* study was established to determine evidence of allergic reactions and/or apoptotic and autophagic markers in blood or organs. Additionally, an *in vivo* proof-of-concept on the therapeutic efficacy of selected formulations was performed in a mouse model of tuberculosis. The results demonstrated the ability of spray-drying to produce aerodynamically adequate microparticles for the purpose of the work, based on the selected polysaccharides. The materials were shown to not induce allergic reactions after lung administration and the *in vivo* proof of concept demonstrated the potential of the inhalable therapy in reducing the infection.

Takeaway Notes:

- Ability of spray-drying to produce microparticles from several polysaccharides, with tailorable aerodynamic properties and high association of drugs;
- Inhalation may be an alternative to oral delivery of drugs, particularly in lung diseases;
- *In vivo* proof of concept helps establishing the potential of designed formulations, in this case providing evidence of the benefits of the inhalable formulation versus the conventional oral antibiotherapy

Biography

Ana Margarida Grenha has received her PhD in Pharmacy-Pharmaceutical Technology from the University of Santiago de Compostela – Spain in 2007. She is Assistant Professor in Pharmaceutical Technology at the University of Algarve in Portugal since 2007 and is a Senior Researcher at both the Centre of Marine Sciences and the Centre for Biomedical Research, at the same University. She is the PI of the Drug Delivery Laboratory, which is dedicated to the design and development of particulate carriers for drug delivery, with a particular focus on inhalation.

She has been the PI of several funded projects, and has authored 33 original papers in international peer-reviewed journals, 5 book chapters and 1 patent in the field of drugs and drug delivery systems.

DAY 2

Keynote Forum

Global Conference on
**Pharmaceuticals and
Drug Delivery Systems**

June 29 - July 01, 2017 | Valencia, Spain

PDDS 2017

Pharmaceutics and Drug Delivery Systems

June 29 - July 01, 2017
Valencia, Spain

Driving endocytosis for enhancing cellular delivery and intracellular targeting of therapeutics.

Arwyn T. Jones *Ph.D*

Cardiff University, UK



Targeting disease processes inside cells with biopharmaceuticals represents a major challenge, not least in overcoming biological barriers such as those posed by the plasma membrane. Investment in this approach is justified when one considers the number individual intracellular targets now available to us as we continue to understand disease processes at the gene and protein level. This is true for many high-burden diseases including cancer, infectious diseases and inherited genetic defects such as cystic fibrosis.

Our research at Cardiff University is focused on studying endocytosis and specifically on designing methods to analyse individual endocytic pathways to characterise how drug delivery vectors and associated therapeutics gain access to cells. As vectors we have paid particular attention to natural ligands, cell penetrating peptides and antibodies. We have focused on their capacity to not only interact with, and enter cells, but also on monitoring their intracellular traffic to reach a final destination.

In this lecture I will describe work we have performed focusing on approaches we have used to study cell binding and endocytosis of drug delivery vectors including cell penetrating peptides, ligand decorated nanoparticles and antibodies targeting plasma membrane receptors on cancer cells. I will highlight how Internalisation of receptors can be significantly enhanced through manipulating ligand and receptor association, and how normal endocytic routes can be modified to reach a desired intracellular location. Our involvement in a €30M FP7 Innovative Medicine Initiative (IMI-EFPIA) consortium (COMPACT www.compact-research.org/) will also be discussed. This represents a public-private collaboration between 14 European academic institutes and pharmaceutical companies aiming to improve the cellular delivery of biopharmaceuticals across major biological barriers of the intestine, lung, blood brain barrier and skin.

Takeaway Notes

- That effective plasma membrane targeting is not always associated with effective internalisation to reach the intracellular target.
- That there is a need for more basic research and understanding of natural mechanisms governing endocytosis of plasma membrane receptors that are selected for therapeutic targeting. Then new drug delivery formulations can be designed to better promote cellular uptake of targeted receptors and modify intracellular targeting to provide the therapeutic cargo with a better chance of reaching its target.
- That ligand valency on nanoparticles designed as drug delivery vectors is critical for not only targeting at the plasma membrane but also in directing endocytic traffic to different subcellular compartments.

Biography

Arwyn gained his PhD in protein crystallography at Birkbeck College, University of London and undertook postdoctoral positions investigating membrane traffic on the endocytic pathway at the University of Liverpool, Harvard University and the European Molecular Biology Laboratory, in Heidelberg. In 2001 he was appointed as lecturer in at the Cardiff School of Pharmacy and Pharmaceutical Sciences at Cardiff University where he is now Professor in Membrane Traffic and Drug Delivery.

Research projects in his lab fall under themes of cancer cell biology, endocytosis and drug delivery. A major scientific objective is linking fundamental endocytosis research to better understand the cellular delivery of drug delivery vectors including antibodies targeting plasma membrane receptors. He actively collaborates with a number of national and international groups including his recent strong involvement with COMPACT (<http://www.compact-research.org/>), an academic/industrial drug delivery consortium collaborating on the Optimisation of Macromolecular Pharmaceutical Access to Cellular Targets.

Pharmaceutics and Drug Delivery Systems

June 29 - July 01, 2017
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Cyclodextrins as reliable solubilization tools for BCS class II and IV drugs

Carmen Popescu Ph.D

Roquette America, USA



In recent years, formulator's attention was focusing on cyclodextrins as a solubilizing tool for their stubborn APIs (BCS class II and IV)). The reason is obvious: easy to scale up and a successful presence of APIs solubilized with cyclodextrins as both liquid and solid dosage form, on the market. This presentation is centered on a coherent approach of insoluble APIs solubilization by cyclodextrin complexation in liquid phase and as solid dispersions (by kneading, spray drying, lyophilization and physical mix) through case studies (carbamazepine, danazol, albendazole, furosemide, zotepine, zaleplon, lorazepam, NSAIDs, etc.). Based on physical and chemical properties of your API, specifically: how many atoms (C, P, S, and N) the skeleton of the drug molecule holds, how many condensed rings, water solubility, melting point temperature, molecular weight, electrostatic charge, log P, pKa, stability issues (chemical, photo, etc.) it is easy to decide if cyclodextrins are the answer to its solubilization. If solubilization optimization is not needed for a good performance of your API and you still wonder "why cyclodextrin complexation?" you should not forget that they can additionally offer: increased stability (physical, chemical), masked taste /odor, convert liquid forms into amorphous powders, new formulation, new routes of administration, patent extension increased shelf life, etc. Cyclodextrins in biotechnology are a very efficient tool in preparation of widespread use of serum-free and chemically defined (CD) media by replacing FBS (fetal bovine serum) by solubilizing cholesterol and fatty acids for supplementation of cell culture.

Takeaway Notes

- Based on physical and chemical properties of your API, dose and route of administration you can decide even in pre-formulation stage if cyclodextrins can solubilize your API
- Identify the type of cyclodextrin and the most efficient process suitable for your API formulation
- Summarize the advantages and cyclodextrin flexibility in liquid and solid dispersions formulation and scaling up processes

Biography

Dr. Carmen Popescu got her B.S. degree in Physics and Ph.D. in Biophysics at University of Bucharest, Romania. She is a Senior Project Coordinator at Roquette America Inc., located in Geneva, Illinois. She came to USA in 1999, as an Associate Professor with University of Illinois at Chicago, College of Pharmacy where she is still an Adjunct Associate Professor. In her career, she focused on the development of classic dosage forms (liquid, semi-solid and solid dosage forms formulation) as well as drug delivery systems (microparticles, nanoparticles, liposomes, niozome) for small and large molecules. She has published over 120 research papers, book chapters and presentations. You can find her publications on: https://www.researchgate.net/profile/Carmen_Popescu3

She is also an Adjunct Associate Professor with Roosevelt University and University of Tennessee. She is teaching in "Tablets & Capsules Hands-on Short Course" at Univ. of Maryland and "Hands-on Tablet Technology Course" at Univ. of Mississippi.

Pharmaceutics and Drug Delivery Systems

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Dry powder inhalers - challenges and opportunities in delivering drugs to the lungs.

El Hassane Larhrib

University of Huddersfield, UK



I will start my presentation by sharing with the audience the importance of particle engineering for different pharmaceutical applications such as oral and inhaled products. In the second part of my talk, I will stress the importance of dry powder inhaler (DPI) devices use and their effect on treatment compliance and disease management in patients suffering from respiratory diseases (e. g. Asthma and Chronic Obstructive Pulmonary Disease [COPD]). Finally, I will be discussing the issues associated with: i) inhalation manoeuvre parameters and drug delivery by DPIs to the lungs; ii) pharmacopoeial methodologies for testing DPIs in-vitro.

Biography

Dr Larhrib was educated at the University of Sciences and Technology, Lille and the faculty of Pharmacy, Lille II, France where he obtained an MSc Biochem, DU Pharm, DESS Pharm. Tech. and a certificate in Pharm. Chemistry. He moved to the UK to do a PhD in Pharmaceutical technology at Liverpool John Moores University, using high speed compaction simulator to fundamentally study the mechanism of compaction of pharmaceutical powders under the supervision of Dr. James Wells and Prof. Mike Rubinstein (1994-1998). Following his PhD, Dr Larhrib worked for 4 years (1998-2002) as Senior Research Fellow in Pharmaceutics at the Department of Pharmacy, King's College London. He worked at Liverpool John Moores University as a Senior lecturer in Pharmaceutics for 6 years (2002-2007) before joining the industry; Solid Solution Limited, Liverpool (2007-2010). He was involved in cosmetic products development and manufacture. He moved to Medway school of Pharmacy before joining the University of Huddersfield as a Senior lecturer in Pharmaceutics in July 2011. Dr. Larhrib is a regular reviewer for many international Pharmaceutical journals and member of editorial board of journal of International Research in Medical and Pharmaceutical Sciences and British Journal of Pharmaceutical Research.

Pharmaceutics and Drug Delivery Systems

June 29 - July 01, 2017
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Crystal engineering of alternative solid forms of therapeutic agents

Mino R. Cairra *Ph.D*

Centre for Supramolecular Chemistry Research, University of Cape Town, South Africa



The physicochemical properties and the performance of both active pharmaceutical ingredients (APIs) as well as new chemical entities (NCEs) can be significantly modified by converting them into different crystalline forms, including polymorphs, solvates, co-crystals and host-guest complexes. In particular, for APIs and NCEs having low aqueous solubility, and consequently poor or variable bioavailability, such solid-state modification can yield new crystal forms with enhanced solubility, facilitating the process of formulating effective pharmaceutical products. In this context, such supramolecular manipulation is recognized as a crystal engineering approach to broadening the solid-state landscape of bioactive molecules, with potential for improving not only the solubility of a drug but additional, pharmaceutically relevant properties such as thermal stability, tableability and reduction of hygroscopicity.

In this presentation, recent case studies involving the generation of multiple crystalline forms of selected APIs and NCEs and the physicochemical characterization of these products will be described. Bioactive compounds that will feature in these case studies include antioxidants, anticancer agents, antivirals, and compounds with antimalarial and anti-tubercular activities.

Key methods used to identify new crystal phases unequivocally and determine their thermodynamic stability include X-ray diffraction, spectroscopic techniques and thermal analysis. The utility of single crystal X-ray diffraction in elucidating the crystal structures of such new phases at atomic resolution will be emphasized, as will the application of powder X-ray diffraction to phase identification and monitoring of phase transformations occurring at different temperatures. Assessment of drug beneficiation resulting from this crystal engineering approach will also be described. Finally, the importance of employing this type of supramolecular intervention at an early stage following drug discovery will be highlighted for its potential to identify the most favourable candidates for further development.

Takeaway Notes

- An appreciation of the fact that compared to ab initio drug discovery, a crystal engineering approach to generating multiple solid forms of poorly-soluble bioactive molecules may be a shorter and relatively inexpensive route to improving pharmaceutically relevant properties.
- That characterization of new solid-state forms of bioactive compounds by X-ray diffraction techniques is essential for unequivocal classification of these forms as polymorphs, solvates, co-crystals, salts, or other molecular entities.
- Early application of crystal engineering of multi-component systems containing bioactive molecules is desirable since it enables the researcher to identify lead compounds that are amenable to supramolecular modification and hence streamlines the process of drug candidate selection.
- At the lowest level, the audience will be better prepared to understand the rapidly expanding volume of literature on the topic of multi-component systems containing drug molecules. For those interested in pursuing research on alternative solid forms of drugs with enhanced properties, the presentation will describe systematic procedures for generating and characterizing them. A more efficient way of using powder X-ray diffraction in the identification of drug complexes will also be demonstrated

Global Conference on

Pharmaceutics and Drug Delivery Systems

June 29 - July 01, 2017
Valencia, Spain

Biography

Following retirement as Chair of Physical Chemistry at the University of Cape Town (UCT), Professor Mino Caira was appointed as Senior Research Scholar in the same Department in 2015. He has served as Director of the Science Faculty's Centre for Supramolecular Chemistry Research at UCT since 2005, where he supervises the synthesis and physicochemical characterization of multi-component solids containing bioactive molecules (active pharmaceutical ingredients, new drug candidates, bioactive natural products, agrochemicals). He has published over 300 research articles in peer-reviewed journals and several reviews on crystal polymorphism, co-crystallization and cyclodextrin inclusion of drugs.

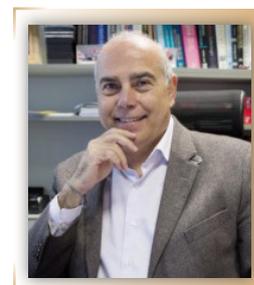
Pharmaceutics and Drug Delivery Systems

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Anionophores, an emerging group of molecules to fight cancer

R. Pérez-Tomás

University of Barcelona, Spain



Eukaryotic life is compartmentalized and the cells have membranes separating the interior from the outside environment. Similarly, the different organelles inside cells are enclosed by membrane. Correct ion exchange through cellular membranes is an essential process for maintaining osmotic balance and intracellular pH (pHi) which are key parameters controlling many biological processes including proliferation, differentiation and apoptosis. Therefore, when cellular pH is not preserved at a favorable level, different pathologies may appear, as it is the case of cancer. Cancer cells undergo a pH deregulation during the process of carcinogenesis, resulting in the acidification of the extracellular pH and the alkalisation of the pHi. Modulation of intracellular pH has recently been proposed as a new therapeutic strategy against cancer. Indeed, prodigiosin, a tripyrrolic natural product with anticancer properties, represents one of the first described anionophores (lipid soluble compounds that facilitate the transport of anions across cell membranes). We have been reported that its biological activity is partly due to its ability to deacidify acidic compartments within cells, which cause a drop in pHi, and therefore the onset of apoptosis described by us in a wide collection of cancer cells. Emulating that characteristic, different anionophores like obatoclax or urea /thiourea group linked to a naphthalimide compounds have been also evaluated by our research group. Recently, we have focused our attention on a novel group of anionophores named synthetic tambjamine analogues, inspired in bioactive marine alkaloids tambjamines. These compounds proved to be very efficient anion exchangers in liposome models, promoting both chloride and bicarbonate transport. We have been able to analyze in detail the molecular mechanism of cell death induced by some selected tambjamines analogues, where ROS production is related with an increased p38 kinase activity as well as a survivin down-regulation following apoptosis induction. Furthermore, we have recently shown the ability of these compounds to hyperpolarize the cellular membrane as well as differentiate and induce cell death in lung cancer stem cells, which are promising properties for their potential use in cancer therapy. Finally in collaboration with a Spanish Biotech company we have developed and assayed a drug delivery system based on innovative polyurethane/polyurea nanocapsules in order to treat more efficiently lung cancer.

This work was partially supported by a grant from the Spanish government and the EU (FIS PI13/00089) and grant from La Marató de TV3 Foundation (20132730) and grant from Junta de Castilla y León (BU09U16).

Biography

Dr. Pérez-Tomás is a full Professor in the Faculty of Medicine at the University of Barcelona. He is the leader of the Cancer Cell Biology Research Group (CCBRG) that is involved in the study of cancer cell biology processes like proliferation or cell death using different cancer models and new bioactive molecules. He has already obtained significant results that offer proof of concept about the idea of using anion transporters as cancer chemotherapeutic agents. Notably, Dr. Pérez-Tomás has authored more than 90 research articles, 3 patents, several conferences and the granting of research projects as PI. He has an accumulated impact factor of 260 and an h-index of 27. He has been director of several works of Master in biomedical experimental science and 8 doctoral theses all of them obtained the highest rating. Dr. Pérez-Tomás is also member of the editorial board of the journals: Current Medicinal Chemistry, Pharmaceutics, Biomedicine and Open Lung Cancer Journal. More information on my research track and interests can be found at: <https://www.ub.edu/cellbiology>

PDDS 2017

DAY 2

Speakers

Global Conference on
**Pharmaceuticals and
Drug Delivery Systems**

June 29 - July 01, 2017 | Valencia, Spain

PDDS 2017

Session on: Formulation Technologies | Preformulation Studies | Biomedicine and Pharmacotherapy

Session Chairs

El Hassane Larhrib

University of Huddersfield, UK

Mino R. Caira

University of Cape Town, South Africa

Session Introduction

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Title: Impact of surface anisotropic forces on powder flowability

M. Teresa Carvajal, Purdue University West Lafayette, USA

Title: Novel ring-fused tetrapyrrolic macrocycles as very active photodynamic agents for cancer

Teresa M. V. D. Pinho e Melo, University of Coimbra, Portugal

Title: Ex-vivo intraocular model to investigate long-term protein stability in vitreous humor

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Title: Development of microparticles loaded with pine bark extracts and evaluation of its bioavailability on fish

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Title: Locust Bean Gum-based nanoparticles for oral immunization

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Sarmad Al-Edresi, University of Manchester, UK

Title: Title: Understanding intestinal permeability: The effect of intestine complexity on oral drug absorption

Arik Dahan, Ben-Gurion University of the Negev, Israel

Lipoprotein based drug delivery platform

Sabnis N. Sood AK, Raut S., Mooberry LK, Lacko AG*
University of North Texas Health Science Center, USA

Although lipoprotein-based drug-delivery was proposed as an outstanding platform for diagnostic and therapeutic applications almost 35 years ago, no lipoprotein based formulations have so far reached the clinical trial stage. Due to small size, long residence time in the circulation and targeted delivery of their payload, several lipoprotein-based formulations have shown a strong potential for translation during pre-clinical studies.

Our laboratory has developed a unique drug delivery platform, reconstituted high density lipoprotein nanoparticles (rHDL NPs), utilizing the ingredients of native HDL. The rHDL NPs are capable of transporting drugs instead of the natural cholesteryl ester payload in the interior core of the lipoprotein complex. The rHDL formulation has shown the capability of tumor selective drug delivery, via receptor (SR-B1 targeted) mechanism and thus the potential for broad application in cancer chemotherapy. In addition, the rHDL NPs are good candidates for repositioning/reformulating of drugs that might have failed clinical trials due to poor solubility and excessive off target toxicity. During pre-clinical studies, the rHDL drug delivery technology has shown the potential for reducing the side effects of cancer chemotherapy. Findings from proof of concept studies will be presented that support the strategy for translation of the rHDL technology toward commercial and clinical applications.

Takeaway Notes:

- Recognition of the value of application of a relatively new technology for commercialization and therapeutic purposes
- The rHDL drug delivery platform is unique because of the stability of the nanoparticles.
- This effect shields the therapeutic payload from interacting with normal cells and tissues.
- Because the drug delivery via rHDL is tumor selective, due to receptor targeting, there is great potential for limiting and perhaps even eliminating treatment related off target effects.

Biography

Dr. Lacko's research focuses on the development and characterization of a lipoprotein based drug delivery system (rHDL), based on a list of beneficial characteristics for rHDL, anticipating this drug delivery model to be superior to existing technologies. Proof of concept studies so far supported these expectations and efforts are under way to translate the rHDL platform toward clinical and commercial applications. Dr. Lacko has published over 100 papers in refereed journals, he has organized several international meetings, has been a reviewer (37 scientific and medical journals and several grant funding organizations). He currently serves on a review panel for the European Research Council.

Impact of surface anisotropic forces on powder flowability

M. Teresa Carvajal

Purdue University West Lafayette, USA

Powder flowability is essential upon handling and during the various unit operations used in the manufacturing of pharmaceutical products. Surface interactions such as cohesive-adhesive contribution depend on the surface composition and particle morphology. The materials used in this study are from different processing conditions having their specific physicochemical properties and surface composition. Various analytical tools were used for having a fundamental insight of the influence that the surface forces have on powder flow. It was found that there were differences in magnitude and extend of the measurable flow by dynamic and static methods. The results obtained on the agglomeration strength suggest that particle properties, material composition as well as microenvironment moisture and shelf life storage (ageing) are responsible for flow performance. These suggests that surface energetics responsible for agglomeration, start with particle adhesive-cohesive interactions, with neck formation due to capillary bridges (moisture presence) and /or to “sintering” (consequence of temperature, glass viscosity, T_g). All contribute to the anisotropic forces that lead to microstructural evolution on the surface of particles that in turn affect powder flowability. The insights of this study at the nano-, micro- and macro-levels will show the relationship between surface anisotropic interactions and flowability of powders that ultimately will help to control and manipulate powder flow.

Biography

Teresa Carvajal is a faculty member of the Agricultural and Biological Engineering department at Purdue University. Dr. Carvajal's research focuses on surface science to assess issues and behavior of powders as a result of the inherent solid state structural, physicochemical, particle surface (interactions e.g. adhesion/cohesion and electrostatics) and mechanical properties. The effects of these properties on powder agglomeration, dispersion and flow could be detrimental on the final pharmaceutical product. Her research interests are on probing surface and bulk properties at the microscopic level to be able to manipulate their characteristics at the macroscopic level and get involved in strategies for controlling behavior of powders. Her experimental approach is to use various techniques thermal, spectroscopic and surface characterization to interrogate materials. Her work on fundamental understanding of the systems extends to design, control and choose appropriate materials for formulation development of powders for inhalation and beverage.

Prior to joining Purdue University, Dr. Carvajal worked in the pharmaceutical industry for 13 years. She worked at Hoffmann-LaRoche (Nutley, NJ) in the area of oral dosage form development. Working on the behavior of powders and powder blends, her activities expanded to research and development of formulations for pulmonary delivery of small molecules and peptides. She later joined Bayer Pharmaceuticals (West Haven, CT) where she was responsible for pre-formulation activities as well as early formulation development for lead compounds of drug discovery. She has been an invited and keynote speaker at various national and international conferences. Dr. Carvajal gives short courses to industry on a various topics in Powder Technology to the USA, Europe and Latin America.

Novel ring-fused tetrapyrrolic macrocycles as very active photodynamic agents for cancer

Teresa M. V. D. Pinho e Melo
University of Coimbra, Portugal

The research team has previously reported the synthesis of a new type of stable 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-fused chlorins and bacteriochlorins via an $[8\pi+2\pi]$ cycloaddition of diazafulveniummethides with porphyrins and chlorins. Absorption spectra of these chlorins and bacteriochlorins revealed intense absorption bands within the therapeutic spectral window, at 650 nm and 730 nm, respectively. Preliminary studies on phototoxicity of some of the compounds in melanoma cells proved this class of compounds to be very active as photodynamic agents against melanocytic melanoma (A375) and amelanotic melanoma (C32) cells. Interestingly, a di(hydroxymethyl)chlorin derivative was particularly active against human melanocytic melanoma cells ($IC_{50} = 31$ nM). Near infrared (NIR) luminescent compounds based on platinum(II) derivatives of 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridine-fused chlorins have also been prepared which proved to be very promising theranostic cancer agents. Further studies have been carried out demonstrating the high potential of these macrocycles in photodynamic therapy of several cancers. In this lecture, further details of this study will be presented and discussed.

Biography

Teresa M. V. D. Pinho e Melo was born in Portugal in 1962. She studied Chemistry at the University of Coimbra, where she graduated in 1985, got her M.Sc. in 1991 and her Ph.D. in Organic Chemistry in 1995. She was Research Fellow at the University of Liverpool (1992-1993). She received her Habilitation in Organic Chemistry in 2003. She is currently Associate Professor with Habilitation at the University of Coimbra. Her research interests are mainly in the area of synthetic and mechanistic heterocyclic organic chemistry. She is particularly concerned with the development of synthetic routes to new bioactive molecules. She has published 120 peer-reviewed papers in international journals and seven chapters in multi-author books.

Ex-vivo intraocular model to investigate long-term protein stability in vitreous humor

Sulabh Patel

F. Hoffmann-La Roche Ltd, Basel, Switzerland

Following intravitreal (IVT) injection of protein-loaded long acting delivery (LAD) system, therapeutic protein remains in vitreous humor (VH) and gets exposed at physiological pH and temperature for significantly longer duration. Therefore, it is of prime interest to study the stability of protein in VH at physiological conditions. However, so far, this has been proven to be very challenging. In previous work, we have shown that isolated VH exhibits unique behavior of pH alkaline shift upon incubation and formation of smaller MW degradation products. Hence, we have successfully developed a customized dual-chamber ex-vivo intravitreal model (Ex-Vit) effective in maintaining pH and osmolality of VH constant throughout study period, thus enabling long-term stability investigations of protein in the isolated VH.

Stability of a model bi-specific mAb (mAb) was evaluated in the isolated porcine VH at 37°C for 3 months. Physical stability of mAb was studied by particle analysis, DSC, SEC, CE-SDS, and microscopically, whereas chemical stability was examined by IEC and LC-MS/MS. The potency (binding affinity) of the protein in the stability samples was estimated by SPR-Biacore. MAb exhibited significantly less fragmentation in VH relative to PBS. Similarly, the loss of binding affinity of mAb was noticeably higher in PBS (~50%) at 3 month time point when compared to VH (~40%). Results indicate that studied mAb exhibited better stability in VH compared to PBS, suggesting that for long-term IVT applications, it would be beneficial to investigate stability in VH instead of PBS.

In summary, newly developed Ex-Vit model is suitable to predict long-term stability of proteins and other molecules following IVT injection. Another perspective of application is to estimate release characteristics from controlled release IVT drug delivery systems.

Takeaway Notes:

- Currently, PBS is considered as a gold-standard to evaluate protein stability or release behavior of therapeutics following intravitreal injection. It is mainly due to the lack of advanced and more predictive in-vitro/ex-vivo models.
- The ExVit model discussed in this talk can be used to predict long-term stability of therapeutic protein in the isolated VH. Hence, the results obtained using ExVit model would be more realistic to the in-vivo situation than the PBS.
- It can be a simple and cost effective experimental tool which can be easily set-up in any lab.
- Accounted to these facts, it can offer tremendous advantage during conventional protein formulation development and also for the development of LAD intended for intraocular delivery.

Biography

Dr. Sulabh Patel has obtained his interdisciplinary PhD (Discipline: Pharmaceutical Sciences and Co-discipline: Chemistry) from the University of Missouri Kansas City, USA in Jan-2014. He then joined University of Basel & F. Hoffmann La Roche (Basel) collaborative Post-Doctoral program. In July-2015, Dr. Patel joined the department of Drug Delivery, Pharmaceutical Technology and Development (Biologics), Europe as a Research Scientist. Currently, his research area is mainly focused on the development of Long-acting delivery of Biologics and small molecules for the treatment of back of the eye ocular diseases.

Development of microparticles loaded with pine bark extracts and evaluation of its bioavailability on fish

M. Sc. Tomás Kappes¹, Ph. D. Berta Schulz², Ph. D. Ariel Valenzuela³, Ph. D. Katherina Fernández^{1*}

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Avoiding wounds in salmon and trout farming systems is an important need of the industry, due their potential production decline effect, caused by decrease of fish meat quality, and the consequent profits loss of the companies. The High frequency of wounds in intensive farming, added to their role in the generation of diseases and the current absence of additives to favor the healing process led us to propose the following solution to this problem. We developed a new fish food additive, which contains natural bioactive components obtained from pine bark, which will generate positive effects on fish health; providing prophylactic protection against diseases and also allowing better and faster healing of wounds. In order to get this objective, we stabilized a natural pine bark (*Pinus radiata*) extract on biocompatible polymers, developing six different microparticles and then we evaluated the bioavailability of two of these formulations in trouts (100-150 g).

Taxifolin is a subunit of flavonol present in *P. radiata* bark extracts, this molecule was chosen as the polyphenolic compounds absorption marker for the *in vivo* tests. In a first stage, the validation of the analytical methodology for the quantification of Taxifolin in plasma was done by HPLC (to ng level). After that, taxifolin quantification in fish plasma was used as marker of extracts bioavailability. The absorption kinetics of the phenolic compounds stabilized in two microparticles types was determined, sampling plasma during 48 h. Results indicated plasma of trout that received microencapsulated extract, reached a taxifolin concentration 25% higher than the ones that received the raw extract, for the same initial dosis of ingest. Also, the release of the active compound was more prolonged over time in the microencapsulated samples, observing levels of taxifolin in the blood for longer periods than the raw extract. No taxifolin was detected after 18 h from the administration of the treatments and no cytotoxic effects were observed on fish. This additive can be a contribution to the development of fish farming in general.

Takeaway Notes:

- To develop new polymeric matrices to immobilize natural compounds, whose developed is scares.
- To use bark, which is a byproduct of forest industry and is considered a waste, for the production of a functional food.
- To know how to evaluate the *in vivo* bioavailability of a natural compound.

Biography

Katherina Fernández, date of birth April 25, 1977. Civil Chemical Engineer (2003) University of Santiago de Chile, Master in Science Engineering (2003), University of Santiago de Chile. Doctor of Science in Engineering (2007), Catholic University of Chile. Actually, she's an associated professor in the Chemical Engineering Department, Faculty of Engineering, University of Concepcion, Chile. Her subjects of study during these 10 years are related to biomaterials, bioactivities and bioengineering. She has more than 25 ISI publications, and several investigation projects running at this moment.

Can antibiotics treat cancer?

Revital Kariv¹ MD, Michal Caspi² Ph.D., and Rina Rosin-Arbesfeld^{2*} Ph.D

¹Sourasky Medical Center, Israel

²Tel-Aviv University, Israel

Colorectal cancer (CRC) is the third leading cause of cancer-related deaths in both men and women, with over 1 million people diagnosed each year. In around 85% of the people suffering from a precancerous condition (colorectal adenomas), malignant transformations (carcinomas) or advanced colorectal cancer the tumor suppressor adenomatous polyposis coli (APC) loses its function. Loss of APC results from sporadic or hereditary mutations in the gene coding for the APC protein and leads to uncontrolled expression of cancer promoting proteins. Part of these mutations are nonsense mutations, that are a substitutions of a single DNA nucleotide that creates a pre-mature stop signal in the mRNA, which leads to translation of a truncated, non-functional protein. If the cells protein translation system could ignore these premature stop codons and “read-through” them, the production of a full-length functional protein will be restored. Some antibiotics, which bind the ribosome, were previously shown to have such a capability however these antibiotics have toxic effects. Using a novel screening system, we have identified several agents capable of inducing ribosomal “read-through” of such premature stop codons. Our results show that different members of the macrolide antibiotic family, can lead to “read trough” of the APC nonsense mutations. Treatment of transgenic mice with an APC mutation with different macrolide antibiotics reduced cancer related phenotypes including intestinal polyps size and number. Based on these promising results, a clinical trial is currently conducted at the Sourasky medical center (in collaboration with Dr. Revital Kariv, Digestive Disease Center Tel-Aviv Medical Center) treating Familial adenomatous polyposis (FAP) patients. FAP is an inherited condition in which numerous pre-cancerous polyps form, mainly in the large intestine, due to germline mutations in the APC gene. If these polyps are not treated they will develop into colorectal cancer. Currently we are treating four patients, and based on our preliminary results we have just received authorization to recruit children and approach other hospitals and medical centers. As we believe that this treatments strategy holds high hopes for both sporadic and hereditary cancer patients, we have begun a large-scale screen aiming and pinpointing the most efficient macrolide that can induce APC nonsense mutation “read-through”

Takeaway Notes:

- This is a study that has moved from basic science into the clinic. I will be discussing repositioning of antibiotics for novel usages such as cancer treatment.

Biography

Rina Rosin-Arbesfeld as a postdoctoral fellow at the LMB-MRC Cambridge UK, started studying the Wnt pathway using different genetic models such as the Drosophila fruit fly. At the Sackler School of Medicine at Tel-Aviv University I expended my research to identify and study new components and mechanistically aspects of the oncogenic Wnt pathway. As a PI I started studying novel connections between Wnt signaling and colorectal cancer (CRC). Recently, in collaboration with the gastrointestinal department at the Sorasky medical center, my basic research work has transform into a clinical trial (NCT02175914)

Peptide-based therapeutics for the treatment of neurodegenerative diseases; challenges and opportunities

Gurevich, EV, PhD, Zhan, X, PhD, Gurevich VV, PhD
Vanderbilt University, USA

Arrestins were discovered as the key players in the desensitization of G protein-coupled receptors (GPCRs) by virtue of specific binding to active phosphorylated GPCRs and blocking further G protein activation. Both receptor-bound and free arrestins also initiate multiple signaling pathways, including mitogen activated protein (MAP) kinase pathways, by virtue of scaffolding the pathways' components. One of the two ubiquitously expressed arrestin subtypes, arrestin-3, is the only isoform capable of activating the JNK pathway. Arrestin-3 can facilitate the activation of JNK family kinases independently of receptor binding. We show that short peptides derived from the JNK3-binding region of arrestin-3 effectively mimic the full-length arrestin-3 protein in the ability to activate the JNK pathway. Further deletion of a few amino acids yields peptides that bind some, but not all kinases in the JNK pathway, thereby recruiting them away from productive scaffolds and inhibiting JNK3 activation via the dominant-negative mechanism. We recently found that arrestin-3-dependent JNK activation is a contributing factor to L-DOPA-induced dyskinesia, a severe side effect of the most commonly used L-DOPA therapy in Parkinson's disease. Potential use of arrestin-3-derived peptides inhibiting the JNK activation as anti-dyskinetic therapy will be discussed. We will also discuss the potential of protein-derived peptides capable of fulfilling select functions of the parent multi-functional protein as therapeutic tools, specifically to target protein-protein interactions, which are notoriously hard to modulate with small molecule therapeutics. Finally, the issue of the best way of delivering the peptide therapeutics into the brain will be addressed.

Takeaway Notes:

- Other faculty could find this research helpful in their own studies of the signaling pathways involved in diseases, since this is a relative novel way to modulate the signaling;
- Our experience in using peptides to treat a brain disease would be helpful to other scientists interested in neurodegenerative and other brain disorders;
- The design of the therapeutics targeting protein-protein interactions could also be advanced by our studies. Since most regulatory functions in the cells are performed via protein-protein interactions, this would help to open up a large pool of novel therapeutic targets that would become "druggable".

Biography

Dr. Eugenia V Gurevich completed her doctorate in neuroscience in Moscow State University. She trained as a postdoctoral fellow with Dr. Jeffrey Joyce at the University of Pennsylvania, Pennsylvania, USA, and then accepted the position as the Brain Bank Director and Staff Scientist at Sun Health Research Institute in Sun City, Arizona, where she conducted research on dopamine receptor functions in Parkinson's disease and schizophrenia with the focus on postmortem studies of the human brain. Since 2003, Dr. Gurevich is a faculty member of the Department of Pharmacology at Vanderbilt University, Tennessee, (Assistant Professor 2003-2009, Associate Professor from 2009), where she conducts research on the regulation of dopaminergic signaling in the normal and diseased brain. She is particularly interested in the functional role of proteins, G protein-coupled receptor kinases (GRKs) and arrestins, controlling desensitization of G protein-coupled receptors in neural pathologies such as Parkinson's disease, L-DOPA-induced dyskinesia, and drug addiction. She is an expert on the use of viral gene transfer technology to induce protein expression or knockdown in the brain of living animals. Dr. Gurevich has pioneered the study of the role of GRKs and arrestins in L-DOPA-induced dyskinesia with the goal of targeting these proteins to control dyskinesia and other L-DOPA-induced motor complications. This work may eventually lead to the development of novel therapies for Parkinson's disease and drug discoveries targeting GRK proteins.

Polymer-based combination therapeutics

Juanjo Arroyo¹, Aroa Duro-Castaño¹, PhD, David Charbonnier^{1,2}, Esther Masía^{1,2}, Vicent J Nebot^{1,3}, PhD, Ana Armiñán, PhD¹, María J. Vicent, PhD^{1,2,3*}
Polymer Therapeutics Lab, Spain
Screening Platform Centro de Investigación príncipe Felipe, Spain
Polypeptide Therapeutic Solutions SL, Spain

Polymer conjugates are nanosized hybrids that covalently combine a bioactive agent with a polymer to ensure not only its efficient release to the required intracellular compartment, but also its availability within a specific period of time. Clinical proof of concept for these multi-component constructs has been already achieved as anticancer agents, both as single agents or as elements of combinations. The fast evolution of polymer chemistry and bioconjugation techniques and deeper understanding of cell biology opened up exciting new opportunities. However, many challenges still lay ahead providing scope to develop this platform technology further. Delivery of new anticancer agents focusing on novel molecular targets and their combination, development of both new and exciting polymeric materials with defined architectures and treatment of diseases other than cancer, in particular looking at promoting tissue repair, are the most exciting and promising areas, and therefore, are the driven research lines in the Polymer Therapeutics laboratory at CIPF.

Our research lines to be discussed during the presentation include the design of novel polymer-based nanoconjugates for the treatment of metastatic tumours as well as the development of novel polymeric carriers and conjugates for neurodegenerative diseases with inherent capability to cross the BBB.

Takeaway Notes:

- General Concepts in Nanomedicine, Drug Delivery and in particular Polymer Therapeutics allowing a rational design.
- I believe all could be apply depending on the particular delivery problem encountered or unmet clinical need to be treated.

Biography

Dr. María J. Vicent is head of Polymer Therapeutics Laboratory at Centro de Investigación Príncipe Felipe (CIPF, Valencia Spain) since 2006. Currently she is also the responsible of the Screening Platform and the Advanced Therapies Program Coordinator at CIPF. She also coordinates the Valencian Community Strategy on Innovative and Precision Medicine. Her research group focused on the development of novel nanopharmaceuticals, in particular Polymer Therapeutics, for different therapeutic and diagnostic applications and has been funded by national and European grants (several acting as coordinator including an ERC Consolidator grant-MyNano). Maria has received several prizes and awards one on her pioneer work on polymer-based combination therapeutics or directly related to a novel platform capable to cross the blood brain barrier with application in neurodegenerative disorders. María co-authored >85 peer reviewed papers and 7 patents, 2 of them licensed to the pharmaceutical industry and a third one used as foundation of the spin off company 'Polypeptide Therapeutic Solutions SL' in 2012.

Hydrogen sulfide: A novel mediator and therapeutic target for inflammatory disease

Madhav Bhatia

University of Otago, Christchurch, New Zealand

Uncontrolled inflammation is responsible for several diseases, which are major health problems. Hydrogen sulfide (H_2S), a gas with the characteristic odour of rotten eggs, has been recognized as an important endogenous gaseous signalling molecule. Our group is the first in the world to show that endogenously produced H_2S , synthesized by Cystathionine- γ -Lyase (CSE), acts as a novel mediator of inflammation. Current research is focused on determining the mechanism by which H_2S contributes to inflammation. Early studies on the mechanism of action of H_2S in inflammation indicate a role of substance P, chemokines, adhesion molecules, MAP kinase ERK, and transcription factor NF- κ B. Most of this research involves working with animal models of disease and in vitro systems. In this research, we have used pharmacological inhibition of H_2S synthesis by CSE, CSE gene deletion, and gene silencing of CSE (by siRNA) as experimental approaches. Recent research points to a role of H_2S in clinical inflammatory diseases. These studies point to H_2S as a novel therapeutic target for inflammatory diseases.

Takeaway Notes:

- The story of H_2S as a novel mediator of inflammation
- How multiple and complementary approaches can be used to understand disease mechanisms
- Evidence that H_2S can serve as a novel therapeutic target for inflammatory disease

Biography

Prof. Madhav Bhatia heads the Inflammation Research Group in the Department of Pathology at the University of Otago, Christchurch. Research in his laboratory has shown hydrogen sulfide and substance P as mediators of inflammation and potential therapeutic targets for inflammatory diseases such as acute pancreatitis, sepsis, burn injuries, and joint inflammation. He has received numerous grants, has authored more than 170 contributions to the peer-reviewed literature, given several invited presentations in different countries and is on Editorial Boards of 34 journals. His publications have been cited more than 8000 times, and he has an "h"-index of 47.

Locust Bean Gum-based nanoparticles for oral immunization

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During the presentation will be discussed the design of nanoparticles based on locust bean gum (LBG) and chitosan to be used as oral immunoadjuvant for vaccination purposes. The advantages of oral immunization and the importance of LBG for this purpose will be explained. LBG-based nanoparticles were prepared by mild polyelectrolyte complexation between chitosan (CS) and a synthesized LBG sulfate derivative (LBGS), thus, this nanoparticle preparation methodology and the LBG derivative synthesis methodology will be addressed. The morphological characterization suggested that nanoparticles present a solid and compact structure with spherical-like shape. Sizes around 180-200 nm and a positive surface charge between +9 mV and +14 mV were obtained. The cytotoxicity of the polymers and nanoparticles will be discussed and CS/LBGS nanoparticles did not affect cell viability of Caco-2 cells after 3 h and 24 h of exposure when tested at concentrations up to 1.0 mg/mL. Two model antigens (a particulate a cellular extract HE of *Salmonella enterica* serovar Enteritidis, and ovalbumin as soluble antigen) were associated to CS/LBGS nanoparticles with efficiencies around 26% for ovalbumin and 32% for HE, which resulted in loading capacities up to 12%. The reason for using these two model antigens will be discussed. The association process did not affect the antigenicity of the associated antigens, confirming the mildness of the nanoparticle preparation methodology. BALB/c mice were orally immunized with ovalbumin-loaded nanoparticles (100 µg), and results indicate an adjuvant effect of the CS/LBGS nanoparticles, eliciting a balanced Th1/Th2 immune response. Therefore, CS/LBGS nanoparticles are promising as antigen mucosal delivery tools, with particular interest for oral administration.

Takeaway Notes:

- The audience will see that unusual polymers can be used to produce nanoparticles;
- The chemistry of these polymers can be tailored to fit the needed characteristics;
- This presentation can give attendees some new ideas that they can implement in their researches.

Biography

Luis Braz is an assistant teacher at Universidade do Algarve since 2007, and was previously a Pharmacy Technician (2000 – 2007) at Hospital de Santa Luzia – Viana do Castelo. At Universidade do Algarve he belongs to the Pharmacy degree course committee since 2010 and has supervised 3 MSc theses of Pharmaceutical Sciences students.

He finished his BSc in Pharmacy in 2001 and the MSc in Chemistry in 2006. He recently concluded the PhD in Pharmaceutical Sciences – Pharmaceutical Technology specialty at Faculdade de Farmácia da Universidade do Porto (2016).

As a researcher, Luis Braz was part of GISOCB – Faculdade de Ciências da Universidade do Porto (02/2003 – 03/2006) and CIQA – Universidade do Algarve (09/2009 – 10/2017), and now integrates CBMR – Universidade do Algarve (11/2017 – present). He has participated in more than 30 national/international congresses with 4 oral and 16 poster communications and published 4 articles in international peer-review journals. His scientific interests focus the use of natural polymers to develop drug delivery systems.

Active loading of resveratrol in transferrin-functionalised liposomes using a pH gradient technique

Sarmad Al-Edresi*, Sally Freeman, Harmesh Aojula, Jeffrey Penny
University of Manchester, UK

Resveratrol, a polyphenol, found in grapes and red wine, has been reported to have many potential therapeutic properties. However, resveratrol demonstrates poor water solubility and short biological half-life, and lacks therapeutic efficacy due to inadequate concentration at the site of action. Resveratrol is a lipophilic compound and could be accommodated, in small quantities, in the lipophilic lipid bilayer of liposomes. The aim of the current study was to substantially improve resveratrol incorporation within liposomes, thereby improving the potential for more effective liposomal delivery of the polyphenol. Liposomes were prepared using the thin film hydration method and active loading was carried out using a pH gradient as a driving force for resveratrol incorporation. Liposomal particle size was analysed by photon correlation spectroscopy and morphology was assessed by transmission electron microscopy (TEM). Small-angle x-ray diffraction (SAXS) analysis was carried out to estimate the thickness of the lipid bilayer. The release profile of resveratrol was also analysed. The level of resveratrol incorporated into liposomes using the active loading technique was significantly higher than that observed with the passive loading approach. The resveratrol encapsulation efficiency under passive loading conditions was 0.6 %, increasing significantly to 33 % with active loading. The liposomes produced were homogeneous spherical particles, with diameters of between 80 – 100 nm. The thickness of the lipid bilayer as measured using SAXS was 8.1 ± 0.3 nm. The release profile of resveratrol was biphasic, which is typical of a sustained release formulation. Active loading using a pH gradient is an extremely promising approach for successfully loading high concentrations of resveratrol into liposomes, and could be applicable for increasing the encapsulation efficiency of other lipophilic compounds.

Takeaway Notes:

- A new technique has been introduced to load a lipophilic drug into liposomes.
- This technique will help other researchers to load any lipophilic drug into liposomes.
- The technique is simple and fast with sufficiently high loading capacity could be achieved.

Biography

Sarmad Al-Edresi is a lecturer at the School of Pharmacy, University of Kufa and a PhD student at the Division of Pharmacy and Optometry, University of Manchester. He was born in Baghdad, Iraq on September 1st 1977. He graduated from School of Pharmacy, University of Baghdad in June 2000. He worked in the General hospital of Bahqoubah, DIALYA, Iraq and completed his Master degree in pharmaceutical technology from School of Pharmacy, University Sains Malaysia in June 2009. Following graduation, he worked as a lecturer in many universities and the last university was University of Kufa, Iraq.

Understanding intestinal permeability: The effect of intestine complexity on oral drug absorption

Prof. Arik Dahan, Ph.D

Ben-Gurion University of the Negev, Beer-Sheva, Israel

In this lecture, regional-dependent intestinal permeability will be discussed, including dissolution aspects, as well as pathophysiological conditions. Permeability is location dependent, and pertains to each point throughout the gastrointestinal tract. A drug may exhibit significantly different intestinal permeability not only between the small and large intestine, but even within the small intestine, i.e. between the proximal jejunum and the distal ileum. The asymmetrical pH profile throughout the small intestine may be the underlying mechanism for such segmental-dependent permeability of certain ionizable drugs. An asymmetrical expression pattern of different transporters throughout the intestinal tract may also cause such regional-dependent permeability. Asymmetrical intestinal enzymes expression may significantly influence the systemic bioavailability of a drug, although not necessarily affect the permeability. In these cases, rapid vs. sustained dissolving drug products may result unexpectedly different systemic drug levels. In conclusion, it is prudent to consider the intestinal permeability pattern when deciding on a certain dissolution profile.

Takeaway Notes:

The audience will learn to consider the intestinal permeability pattern along the whole gastrointestinal tract when deciding on a certain dissolution profile for a given drug candidate; the audience will be able to implement these principles to develop optimal drug exposure following oral administration.

Biography

Arik Dahan is an Associate Professor of Pharmaceutics and Biopharmaceutics at the Department of Clinical Pharmacology and the School of Pharmacy, Ben-Gurion University of the Negev in Beer-Sheva, Israel. He is also an Adjunct Professor of Pharmaceutical Sciences at the College of Pharmacy, University of Michigan, USA. Dr Dahan received his Ph.D. (2007) from the Hebrew University of Jerusalem. From 2007 until 2009 he was a Post-Doctoral Research Fellow at the University of Michigan College of Pharmacy with Professor Gordon Amidon. Dr Dahan's research interest is the integration of up-to-date molecular and cellular mechanistic investigations of drug disposition in the context of the human body, in order to enable successful drug delivery and therapy. In implementing this molecular biopharmaceutical approach to ADME research, Dr Dahan is seeking to enable mechanistic-based successful solutions to drug delivery, especially (but not only) oral, in challenging scenarios e.g. low-solubility, low-permeability, efflux transport, extensive metabolism, poor site targeting, various pathophysiological conditions (e.g. obesity, inflammatory bowel disease), and pediatrics patient care. He has authored over 70 top-notch Journal papers, and contributed chapters to 7 books.

Poster Presentation

Global Conference on
**Pharmaceuticals and
Drug Delivery Systems**

June 29 - July 01, 2017 | Valencia, Spain

PDDS 2017

Poster Presentations

- P1 Oral delivery of a novel antibody domain (Vorabody™) for the treatment of Crohn's Disease**
John Wahlich, John Wahlich (VHsquared Ltd), UK
- P2 Sustained and/or controlled delivery by core-shell polymer nanocapsules**
Gemma Vilar, Leitat Tecnological Center, Spain
- P3 Development and evaluation of nanofibrous oral strips – new drug delivery system for poorly soluble drugs**
Anna Kluk, Zentiva k.s, Czech Republic
- P4 Absorption enhancing capacity of dissolving microneedle arrayed patches**
Booyong Lee, Raphas Co., Ltd, Republic of Korea
- P5 The effect of the inhalation manoeuvre parameters on the indacaterol drug deposition from Onbrez Breezhaler dry powder inhaler**
Mohamad Abadelah, University of Huddersfield, UK
- P6 The applications of potential aromatic prodrugs in NTR based cancer therapy**
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- P7 A Pre-formulation study of recombinant human interleukins-1 receptor antagonist for emergency use**
Amal Abukhares, University of Manchester, UK
- P8 Design and synthesis of new EF2K inhibitors for the treatment of TNBC and pancreatic cancers and their in vitro release studies from biocompatible natural polymeric particles**
Ferah Comert Onder, Canakkale Onsekiz Mart University, Turkey
- P9 Method indicative of stability for determination of rifaximin and its degradation products by thin chromatographic**
Ana Carolina Kogawa, Univ Estadual Paulista – UNESP, Brazil
- P10 Comparison of UV, IR, CE, HPLC and turbidimetric methods in the evaluation of rifaximin**
Ana Carolina Kogawa, Univ Estadual Paulista – UNESP, Brazil
- P11 Polyphenols loaded vaginal microbicide: A novel strategy for prevention of HIV transmission**
Amit Mirani, Institute of Chemical Technology, India
- P12 Nanoparticle Engineering of atovaquone using nano-by-design (NbD) approach**
Pratik S. Kakade, Institute of Chemical Technology, India
- P13 Analytical method development and validation of End-LAA for in vitro and in vivo studies**
Cansel Kose Ozkan, Gulhane Education and Research Hospital, University of Health Sciences, Turkey

Oral delivery of a novel antibody domain (Vorabody™) for the treatment of Crohn's Disease

John Wahlich, Gary Whale, Tim Carlton, Scott Crowe, Marion Cubitt, Luana Maggiore, SuhailNurbhai, Kevin Roberts, Jan Robinson, Mike West
John Wahlich (VHsquared Ltd), UK

Only very few oral peptides have been commercialised to date, these include cyclosporin A (Neoral®) for the treatment of transplantation rejection; desmopressin (DDAVP®) for the treatment of nocturnal enuresis and linaclotide (Linzess®) for the treatment of irritable bowel syndrome with constipation). Each of these is a relatively small biomolecule (< 2K Daltons), each has a cyclic structure which confers stability and in the case of desmopressin is active at very low doses such that the ensuing poor bioavailability is not an issue. To date the challenge of delivering more complex proteins orally has not been met.

Crohn's disease (CD) is a chronic inflammatory condition which can affect any part of the gastro intestinal tract (GIT) but most commonly occurs in the lower part of the ileum and in the colon. This and ulcerative colitis make up the majority of cases of inflammatory bowel disease (IBD). The aetio-pathogenesis of Crohn's disease is not fully understood but genetic and environmental factors interact to promote an excessive and poorly controlled mucosal inflammatory response against components of the gut micro-flora. Inhibiting the pro-inflammatory cytokine tumour necrosis factor (TNF) dramatically reduces gut inflammation and thereby restores the gut barrier and promotes healing.

Current biologic anti-TNF treatments for Crohn's disease include adalimumab (Humira®); certolizumab pegol (Cimzia®) and infliximab (Remicade®). All of these have to be administered by injection. VHsquared Ltd has successfully engineered a protease stable domain antibody to TNF (V565, molecular weight 12.6K Daltons) which is the lead compound of the VHsquared Vorabody™ platform technology and has been shown to be effective in neutralising TNF in vitro and inhibiting its effect in biopsies from patients with Crohn's disease. Unlike existing treatments it has been designed to be administered orally and is currently in Phase 2 clinical trials.

Developing an oral protein formulation for the treatment of Crohn's disease presented a number of challenges: stabilising the protein to resist the proteolytic enzymes present in the upper part of the GIT whilst retaining the anti-TNF binding activity; producing a formulation to protect the protein from the acid in the stomach; minimising the risk of dose dumping and the effect of food; and targeting the appropriate section of the GIT. Details are provided of the nature of the challenges in each of these areas and this poster describes how each of these challenges was tackled and how proof was obtained, using a number of novel in-vitro, in-vivo and ex-vivo approaches, that they have been successfully overcome.

Takeaway Notes:

- A better understanding of the challenges in developing an oral protein product. This topic is gaining more and more exposure as the number of biological molecules in development increases
- Formulation designs to provide enteric protection, minimise a food effect and target a specific region of the GIT
- Knowledge of in-vitro, in-vivo and ex-vivo approaches to confirm in-vivo protein stability and that the molecule has reached its intended target in the GIT

Biography

John Wahlich has worked as a consultant in the pharmaceutical sciences for over 5 years. Prior to this he had over 30 years' experience in product development in the pharmaceutical industry. John is a chemist by training with a Ph.D. in the pharmaceutical sciences from Nottingham University School of Pharmacy, UK. He has analytical and formulation expertise gained from leadership roles in product line extensions, physical properties and early stage development in GlaxoSmithKline and other major pharmaceutical companies. He is a member of the UK Association of Pharmaceutical Sciences (APSGB) Executive. He currently works as a consultant for VHsquared, Cambridge, UK and for a number of other pharmaceutical organisations.

Sustained and/or controlled delivery by core-shell polymer nanocapsules

Gemma Vilar*, Ph. D., Eloy Pena, MsC., Lorena García, Ph. D., Socorro Vázquez-Campos, Ph. D
Leitat Technological Center, Spain

Nanoparticles are an important tool to overcome the administration of drugs, improving the pharmacokinetics of active compounds and avoiding their undesired effects. Specifically, nanoencapsulation offers some advantages such as, protection of the active ingredient from other chemicals or biomolecules present in the final formulation, protection after administration and offers possibilities for controlled release of the different active ingredients.

In this presentation, the design and synthesis of biodegradable polymeric nanocapsules for the control of drug/ active ingredient (API) release at the target organs will be described. Tailoring the physical-chemical properties of polymeric nanocapsules allows control over the release of the drug eluting systems, which can be modulated over time and/ or tuning the polymer chemical structure to control the release by external stimuli. Therefore, a set of safe and biodegradable nanocapsules have been developed, in particular core-shell nanocapsules with an average size of 350 nm. In all cases, the core consists of a polyester polymer which is at the front line of attention because of their attractive safety profile. Since their degradation products are easily metabolized by the Krebs cycle and therefore easily eliminated. The different composition of the shell will provide the desired properties, allowing different drug/ API release kinetic.

These core-shell nanosystems will be presented showing their potential in the area of drug delivery systems. Furthermore, encapsulation of different APIs will further demonstrate the different release profiles in relevant biological systems.

Takeaway Notes:

- The audience should be able to see the importance of having the control over such versatile systems to improve current problems with drug pharmacokinetics.
- This work provides novel solutions for those drugs/ APIs that need to be encapsulated due to their chemical and biological properties.

Benefits:

- Drugs/ APIs which need to be incorporated to a final formulation and be stable in it
- Drugs/ APIs which are not stable in the body (chemical and/or enzymatic degradation)
- Avoid the accumulation of the drug/ API in other organs
- Controlled release kinetics
- Sustained release kinetics
- Reducing the dosage frequency
- Avoiding undesired effect of the drug/ API

Biography

Dr. Gemma Vilar is senior researcher in the Human & Environmental Health & Safety in the R&D department of LEITAT Technological Center. She coordinates R&D projects in the nanomedicine and nanobiosensors group, focused on developing both nanoencapsulated systems as organic and inorganic nanoparticles for biomedical applications.

She holds two degrees in chemistry (2005) and biochemistry (2011) from the University of Barcelona. She has done two Masters, one of them about organic chemistry (2005, University of Barcelona) and the other one about the development of polymeric nanoparticles (European Mater, 2007, University of Barcelona). She acquired the Diploma of Advanced Studies (DEA, 2008, University of Barcelona) and completed her studies performing a PhD in nanotechnology (2011, University of Barcelona). She has undertaken several research placements in Valencia, Germany and Canada. She has participated in national and international congresses and is author or coauthor in various prestigious scientific journals.

Development and evaluation of nanofibrous oral strips – new drug delivery system for poorly soluble drugs

Anna Kluk Ph.D.^{1*}, Pavel Sedláč¹, Pavel Hanzlík¹, Petr Mikeš Ph.D.², Aleš Šaman²

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²Technical University of Liberec, Studentská 1402/2, Liberec, Czech Republic

Orodispersible films (ODFs) have recently gained much attention as a very beneficial formulation for pediatric and geriatric patients, where the difficulty of swallowing of the standard solid drug forms needs to be eliminated. Orodispersible films either disintegrate quickly in the oral cavity to be swallowed easily or stay in the particular place in the mouth due to their mucoadhesive properties. Thus ODFs are used as rapid release products and as buccoadhesive or swallowed controlled drug release systems.

One of the most recent method of ODF production is electrospinning - a process, where polymer nanofibers (diameter from few nanometers to several micrometers) can be produced using an electrostatically driven jet of the polymer solution or melt. The main advantage of nanofibrous oral strips is an increased bioavailability of poorly soluble drugs as a result of API conversion from crystalline to amorphous form, incorporated into polymeric nanofibers. Additionally, due to the porous structure of polymeric nanofibers, obtained ODFs (in comparison with products obtained by casting method) demonstrate favorable properties, including homogeneity of thickness and assay, faster disintegration and immediate dissolution.

However, one of the most important requirements of electrospinning is to prepare the final formulation in the form of solution. When using water-soluble polymers water can be applied as solvent in the electrospinning process, however, it is not sufficient to dissolve poorly soluble drugs. The present study relates to the composition of the solution used for electrospinning process in order to prepare orodispersible films as well as the composition of ODFs, comprising poorly soluble therapeutic agents. Preparation of the stable solution, stabilization procedures and effective taste masking have also been proposed.

Takeaway Notes:

- Familiarization with the requirements and details of the new potential production method for oral drug forms
- Example of innovation and “out of box” thinking in the design of drug delivery systems
- Example of an effective taste masking method and amorphization technique of poorly soluble drugs

Biography

Anna Kluk Ph.D. is a graduate of the Faculty of Pharmacy, Medical University in Gdansk, Poland. Her 5-year studies have been dedicated to the design, development and evaluation of modern pediatric drug forms and evaluation of their acceptability in pediatric population during clinical trials. During her Ph.D. studies she was a grant researcher in research projects of Ministry of Science and Higher Education and teacher of pharmaceutical technology and biopharmacy to pharmacy students and postgraduates working in pharmacies and in the pharmaceutical industry. In her current role, she is working in the pharmaceutical industry on the position of Formulation Scientist Junior in Zentiva k.s., Sanofi Company Group, being responsible for the design and development of generic drugs.

Absorption enhancing capacity of dissolving microneedle arrayed patches

Booyong Lee*, Hong Kee Kim, Ph.D., Jung Dong Kim, Ph.D., Jung Hyun Bae, Yang Gi Lee, Moon Su Lee, Tae Hyung Kim, Seong Jin Kim, Na Keum Jang, Do Hyun Jung, Ph.D

Raphas Co., Ltd, Republic of Korea

The microneedle-mediated transdermal delivery system has been developed to provide minimal invasive self-administration method with patient friendly manner. Especially, dissolving microneedles, which deliver the target drugs as the drug-loaded microneedle or medical device to enhance absorption dissolves into the skin, have been developed recently. Conventional dissolving microneedle fabrication methods, stepwise casting method in 3D molds, have problems to standardize the drug dose and to maintain the activity of labile drug during the manufacturing process. Droplet-born air blowing (DAB) method has great advantages in stability with precise dose control because DAB provide quick manufacturing process with ambient temperature. The purpose of this study is to show the characteristics of dissolving microneedles as medical device, which manufactured in our mass production system.

Microneedle fabricated by DAB (Droplet-born Air Blowing) method. Briefly, Biodegradable polymer such as HA (hyaluronic acid) was dissolved in distilled water with active ingredient (in case of drug-loaded microneedle). The polymer was dropped to patch, and each droplet is shaped to the microneedle. The loaded amount of AA2G (Ascorbic Acid 2-Glucoside) was analyzed by HPLC/UV system (Waters, e2695).

And, Skin permeability of microneedle was confirmed by OCT (optical coherence tomography) and delivered amount of drug into the skin was analyzed using Franz diffusion cell (Logan, FDC-6T).

We optimized the DAB process parameters and scaled up. 350 μm length of microneedles were fabricated and dried within 10 min without applying any heat or uv light which could cause any degradation of active ingredient. The active ingredient was stable within microneedle during 2 months at 25 $^{\circ}\text{C}$ and 45 $^{\circ}\text{C}$.

In vitro studies of skin permeability as drug-loaded microneedle using Franz diffusion cell showed excellent delivery efficiency compared to topical solution. Most of the loaded anti-oxidants was delivered through the skin after 24hr (98.0 \pm 2.0%, n=3). The microneedles dissolution in skin was confirmed, so the drugs within microneedle should be delivered into the intradermal region.

For analyzing characteristics of absorption enhancement as medical device, Betamethasone valerate ointment (0.57 mg/ml in ethanol) was applied on the 3D skin model (Strat-MTM, EMD Millipore Corporation, Germany). Dissolving microneedle patch was applied onto the 3D skin model after betamethasone valerate solution application to measure the delivery efficacy of betamethasone valerate using franz diffusion cell.

In vitro studies using Franz diffusion cell showed excellent delivery efficiency about 2.5 times compared to applying only ointment (Betamethasone Valerate).

Takeaway Notes:

- Optimized DAB (Droplet-born Air Blowing) process
- High skin permeability of API (cosmetic ingredients) as drug-loaded microneedle
- To enhance API (ointment) absorption into skin by microneedle arrayed patch
- Suitable skin permeability assay design for microneedle arrayed patch application

Biography

Booyong Lee has done Master's Degree in Electrical and Electronic Engineering from Korea University. And now he is working as a formulation researcher in Raphas. Currently, he is developing dissolving micro needle array, which is based on Pharmaceuticals, and analyzing its characteristics. Field of application of the dissolving micro needle is skin to delivery active ingredients.

The effect of the inhalation manoeuvre parameters on the indacaterol drug deposition from OnbrezBreezhaler® dry powder inhaler.

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²Inhalation Consultancy Ltd, Yeadon, Leeds, LS19 7SP, UK

Dry powder inhalers (DPIs) have been traditionally developed based on in-vitro testing with a square-wave airflow profile as described in the Pharmacopoeia (USP, 2014). Several studies showed that the Pharmacopoeial flow profile is a poor approximation to reality in some important aspects. For example, humans are not able to replicate the square wave generated by a vacuum pump; nor can the majority of patients achieve the pharmacopoeia-recommended inhalation parameters for the change in the pressure inside the inhalation channel of the inhaler or the inhaled volume (Azouz et al., 2015).

Breathing simulators, machines designed to generate and apply an inhalation and/or exhalation profile that mimics that of a human subject, are becoming an increasingly routine part of orally inhaled product (OIP) testing. The breathing simulators have opened up opportunities to improve the clinical relevance of in vitro OIP testing techniques. Recently, researchers are starting to use real patient's inhalation profile (IP) measured during real-life use when an individual uses an inhaler (Olsson et al., 2013). The IP is subsequently replayed through the inhaler in-situ (Olsson et al., 2013) in order to fully scope DPIs product performance (Olsson et al 2010). This ex-vivo method, using a patient inhalation profile instead of the vacuum pump, provides information on the total emitted dose (TED) and particle size distribution (which includes the mass median aerodynamic diameter [MMAD] and the geometric standard deviation [GSD]) that the patient would have inhaled (Chrystyn et al., 2015). The IP generated by the IP recorder has a bell-shape but they differ from patient to patient in terms of the acceleration rate (ACIM), maximum inhalation flow (MIF) and inhaled volume (Vin) (Chrystyn, 2003; Chrystyn 2006; Azouz et al., 2015) depending on patient's lung capacity and disease state. These parameters have been mentioned to affect the clinical effectiveness of the inhaled aerosol, but which one of these parameters is the most important it's still unclear.

This study was designed to assess the effect of Vin and ACIM on the aerodynamic characteristics of indacaterol dose emission from Onbrez Breezhaler® using a fixed MIF of 85L/min.

The profiles were generated when patients with different chronic obstructive pulmonary disease (COPD) severity aged 55-79 with a mean age of 66 inhaled through an empty (Placebo) Onbrez Breezhaler® inhaler device. The patients have read the patient information leaflet (PIL) and they were also trained how to use the inhaler device according to the manufacturer recommendations as described in the PIL. The profiles were recorded when patients inhale as fast as they can through the inhaler. For this study, 9 inhalation profiles were used to assess the effect of each inspiratory parameter on the aerodynamic characteristics of indacaterol emitted dose. Breezhaler is a low resistance device characterized by its low intrinsic resistance value of 0.07 cm H₂O (½)/L/min (Pavkov et al., 2010), thus patients were able to achieve a high flow rate through the device with a mean MIF of 88 L/min. The inhalation manoeuvre parameters generated by patient inhalation such as acceleration rate, MIF, and Vin have been shown to affect drug delivery to the lungs (Laube et al., 2011). Three different Vins (1, 2 and 3L) and three ACIM were used (2, 4 and 8 L/s²) at a fixed MIF of 85L/min (figure 1). The inhalation time was either increased or decreased to achieve the desired Vin. The ACIM was modified by increasing the steepness of the slope, whereas the MIF was the one generated by the patient.

The experimental set-up was adapted to connect the breath simulator (BRS) with Andersen cascade impactor (ACI) via the mixing inlet, through which a supplementary air flow was introduced to achieve 0 L/min at the mouth piece, the ACI was assembled to be used at 90 L/min flow rate (Olsson et al., 2013; Nadarassan et al., 2010).

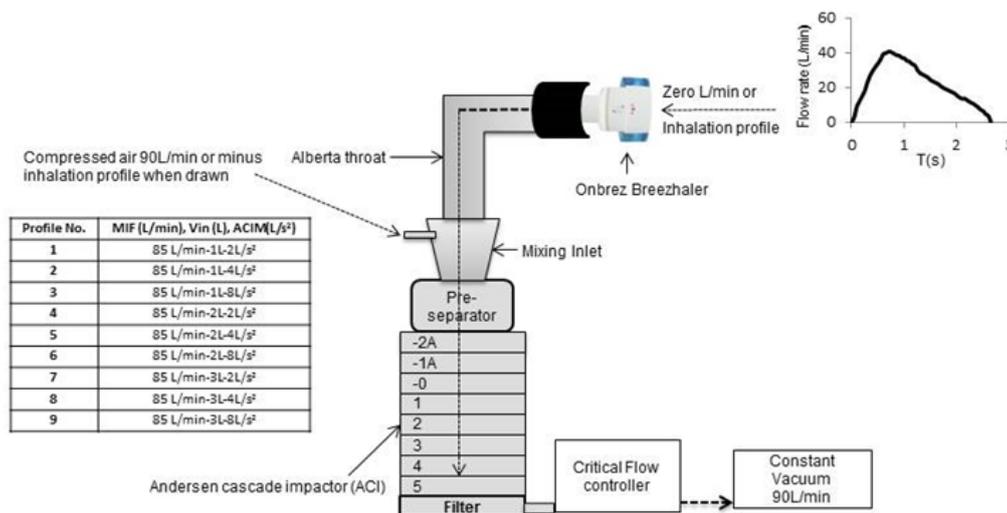


Figure 1: Schematic diagram of the modified ACI methodology with mixing inlet illustrating how patient's inhalation profiles were replayed by breath simulator using Onbrez Breezhaler®

The results showed that increasing the ACIM has significantly ($P < 0.05$) increased the fine particle dose (FPD) for all Vins used, however, the effect of ACIM on the total emitted dose (TED) was more pronounced when 2 and 3 L Vins were used. Residual amount (RA) decreased significantly ($P < 0.05$) when ACIM increased for all Vins used.

The mass median aerodynamic diameter (MMAD) decreased when Vin increased, furthermore, the ACIM was found to have an impact on the MMAD when combined with high inhaled volume 2 and 3 L.

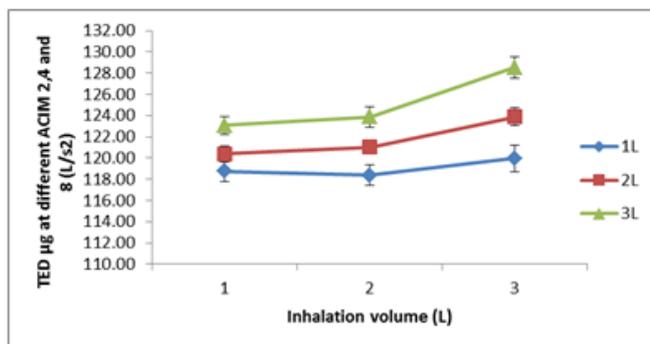


Figure 2: Mean (SD) of Total emitted dose (TED)

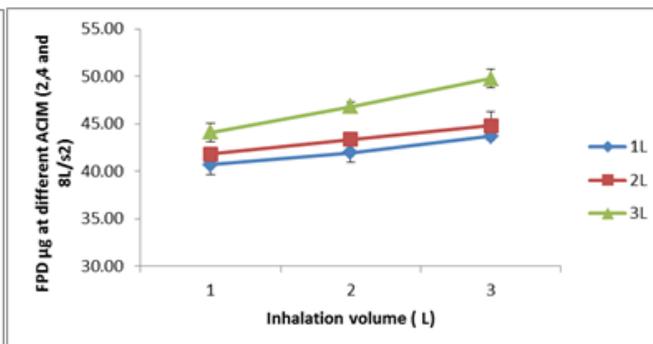


Figure 3: Mean (SD) of Fine particle dose (FPD)

The extra fine particle dose (EFPD $\leq 3\mu\text{m}$) has significantly increased ($P < 0.05$) when inhaled volume increased from 2L to 3L. When 3L inhaled volume was used, an increase in the ACIM showed a significant effect on the EFPD.

Table 1: Mean (SD) of the aerodynamic characteristics of indacaterol emitted dose at different ACIM 2, 4 and 8 L/s² and fixed inhaled volume 1L and MIF 85L/min. (% = percentage of nominal dose 150µg).

Aerodynamic Characteristics	85L/min- 1L-2 L/s ²	85L/min- 1L-4 L/s ²	85L/min- 1L-8 L/s ²
TED (µg)	118.77 (1.01)	118.39 (0.97)	119.95 (1.24)
FPD (µg)	40.70 (1.05)	41.96 (0.98)	43.68 (0.21)
RA (µg)	18.89 (3.03)	18.72 (2.12)	16.30 (0.70)
MMAD (µm)	2.77 (0.06)	2.90 (0.00)	2.75 (0.07)
%EFPD	22.17 (0.54)	20.57 (0.31)	21.94 (1.22)

Table 2: Mean (SD) of the aerodynamic characteristics of indacaterol emitted dose at different ACIM 2, 4 and 8 L/s² and fixed inhaled volume 2L and MIF 85L/min.(% = percentage of nominal dose 150µg).

Aerodynamic Characteristics	85L/min- 2L-2 L/s ²	85L/min- 2L-4 L/s ²	85L/min- 2L-8 L/s ²
TED (µg)	120.41 (0.76)	121.01 (0.38)	123.89 (0.81)
FPD (µg)	41.82 (0.16)	43.35 (0.34)	44.82 (1.51)
RA (µg)	17.18 (0.62)	16.42 (1.21)	14.79 (0.67)
MMAD (µm)	2.90 (0.00)	2.80 (0.00)	2.70 (0.00)
%EFPD	20.23 (0.84)	21.55 (0.38)	22.96 (0.21)

Table 3: Mean (SD) of the aerodynamic characteristics of indacaterol emitted dose at different ACIM 2, 4 and 8 L/s² and fixed inhaled volume 3L and MIF 85L/min.(% = percentage of nominal dose 150µg).

Aerodynamic Characteristics	85L/min- 3L-2 L/s ²	85L/min- 3L-4 L/s ²	85L/min- 3L-8 L/s ²
TED (µg)	123.08 (0.86)	123.88 (0.98)	128.54 (1.03)
FPD (µg)	44.13 (0.98)	46.80 (0.48)	49.76 (0.96)
RA (µg)	18.57 (0.83)	16.03 (1.61)	13.19 (0.64)
MMAD (µm)	2.90 (0.00)	2.75 (0.07)	2.60 (0.00)
%EFPD	21.56 (0.84)	23.35 (0.20)	26.10 (0.18)

In conclusion, the study illustrated the effect of the Vin and ACIM on the indacaterol 150 µg aerodynamic characteristics dose emission from Onbrez Breezhaler®. Modifying the inhalation profiles by fixing two parameters and changing one parameter at a time provided an in-depth understanding on the effect of each inspiratory parameter on drug delivery to the lungs Ex-vivo.

MMAD, FPD, RA, and TED were all influenced by the Vin, however, ACIM has a more pronounced effect on the MMAD,

FPD, RA and TED only at high Vins (2 and 3 L). This ex-vivo methodology, using a patient inhalation profile rather than the vacuum pump, provided information on the TED that the patient would have inhaled in real life.

Main points the study highlighted:

- 1) The patient inhaled volume and the acceleration rate, are as important as the maximum inspiratory flow rate to maximise drug lung deposition.
- 2) The study was an extension of the previous performance study where all three inhalation manoeuvre parameters acted together. Altering the IP to study each inhalation parameter at a time provided more detail on the importance of each inhalation manoeuvre parameter with regards to drug lung deposition.
- 3) The patients using capsule based device should follow the information in the PIL and inhale as fast and hard as they can and prolong their inhalation to get the more clinical benefit for each inhaled dose.
- 4) Finally, inhalation profiles are more representative of the real life dose emission and the amount the patient would have received when inhaling through Onbrez Breezhaler.
- 5) The above results will help to train the patient on how to use their inhaler device correctly to achieve the desirable therapeutic effect.

Biography

Mohamad Abadela has completed his degree in Pharmacy before joining the University of Huddersfield in 2011 to study for a Master degree in the pharmaceutics and pharmaceutical analysis. After completing his master degree with a distinction he decided to pursue his Ph.D. in the inhalation field under the supervision of both Prof Chrystyn and Dr. Larhib. Mohamad's work focuses on dose emission aerodynamic characteristic from dry powder inhalers (DPIs) and evaluation of the performance of some commercially available DPIs on the market. Mohamad's has recently submitted 2 manuscripts for publication in the international journal of Pharmaceutics (IJP) and also presented his research work nationally and internationally at different conferences including UK Pharm.Sci, AAPS, DDL and ERS. Mohamad is also involved in teaching and supervision of undergraduate and MSc research projects in the pulmonary drug delivery.

The applications of potential aromatic prodrugs in NTR based cancer therapy

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Nitroreductase enzymes catalyze the conversion of the nitro group of prodrug compounds via hydroxylamine to amine group and the active drug inhibits tumor formation by binding to DNA. E. coli NTR/CB1954 (5-aziridinyl-2,4-dinitrobenzamide) is the best known combination that have studied phase I/II trial for different cancer types. So more effective NTR/drug combination should be investigated for cancer therapies.

In this study, first of all, we explored and characterized two novel nitroreductases (Ssap-NtrB-cloned from a mesophilic microorganism and Gk-Ntr-cloned from a thermophilic microorganism) with enhanced activity-selectivity and implemented various applications. And nitro group containing two potential prodrugs (isoxazole derivatives and 3,5-difluorophenyl derivatives) were synthesized and were investigated the interaction of these potential pro-drugs with NTR enzymes by spectroscopic techniques and HPLC analysis. Michaelis-Menten kinetic parameters were calculated for reduction reactions of prodrugs and compared common known prodrugs like as CB1954 and SN23862. The prodrugs were evaluated by MTT and SRB assay in three different cancer cell lines, Human Hepatoma Cancer (Hep3B), Human Colon Cancer (HT-29) and Human Prostate Cancer (PC3) in addition to non-cancer cell, HUVEC. According to our results, proposed enzyme/prodrug combinations may use NTR based cancer therapy.

Takeaway Notes:

- Learn the importance of nitroreductase to drug design and other applications,
- Synthesis of new prodrug candidates,
- Design new projects with collaboration for cancer therapy.

Biography

Dr. Tuğba Güngör graduated as BSc at Chemistry Department of Ankara University in 2007 and graduated as MSc in in 2010 under supervision of Dr. Mustafa Güllü and PhD in 2016 at Chemistry Department of Çanakkale Onsekiz. Mart University under supervision of Dr. Mehmet AY. During the PhD education, worked at Dr. Rich Carter's Research Lab. at Chemistry Department of Oregon State University at USA for 6 months at 2015. Since 2011, works as a research assistant at Chemistry Department of ÇanakkaleOnsekiz Mart University and going on research activities in Natural Products and Drug Research Laboratory, focusing on developing new prodrug and drug molecules for Cancer Therapy and other Medicinal Applications.

A Pre-formulation study of recombinant human interleukins-1 receptor antagonist for emergency use

Amal Abukharies

University of Manchester, UK

Introduction: rhIL-1Ra is a recombinant form of the natural anti-inflammatory mediator, interleukin-1 receptor antagonist that competitively binds with type I receptors (IL-1RI). It inhibits effects of other inflammatory mediator, interleukin -1 (IL-1). The product is licensed on 2013 to treat Rheumatoid Arthritis. There is preclinical evidence to suggest that IL-1Ra can be a promising candidate to treat brain stroke. Treatment with Kineret® results in reduced levels of inflammatory markers in plasma of stroke patients and the cerebrospinal fluid and plasma of patients with subarachnoid haemorrhage. However the Kineret® has stability problems at ambient temperature and is hence stored at 2°C to 8°C. In addition, the manufacturer (Amgen PLC) recommends avoiding shaking, freezing and exposure to sunlight. These recommendations for storage are incompatible if the formulation is to be used treat brain stroke outside hospital settings, particularly by paramedic staff in ambulances. It would be advantageous to treat stroke rapidly through intervention by paramedics. This would minimise brain damage from the first sign of stroke.

Aim: The overall project aim is to study thermal stability of the IL-1Ra and identify the root cause of instability. This would lead to designing a suitable pre-formulation to address concerns with storage at ambient temperature.

Methods: Initially, visual inspection (photographs) was made following the incubation of Kineret® at 37°C. Then, the aggregation was followed quantitatively by recording changes in the optical density at 450 nm (OD450 nm). A more sensitive technique was also used to follow aggregation in the nucleation phase, where sub-visible particles may exist, using Dynamic light scattering (DLS). The formation of non-native β -structure of the protein was followed by use fluorescence spectroscopy using Thioflavin T (THT). Attempts were also made, using circular dichroism (CD), to assess any induced changes in the secondary structure of the protein induced thermally.

Conclusion: Our study from suggests that formulation shows visible signs of cloudiness within 6hrs at 37° C. When this is followed by light scattering over 24hrs period a number of kinetic phases due to aggregation were observed starting with a nucleation phase where the changes in particle size were confirmed by DLS. Protein content show a trace amount of protein was aggregated. Fluorescence assay in particular the Thioflavin T result provides earlier indication of formation of non-native beta structures. Therefore, further study will be conducted to characterise protein aggregates.

Biography

Amal obtained her first degree in Pharmacy from the University of Tripoli, Libya 2004-2005. In 2006 she starts to work at University of Tripoli as teaching assistant (demonstrator). She is involved in the supervision of undergraduate students in the assistance for the smooth running of the laboratories. In 2007 she has received funding from her University to finish her post-graduation study, under Libyan grant agreement of 701/2007. In September 2010 she completed her Master degree in drug delivery from Aston University/UK. Between 2011 and 2014 she worked as lecturer assistant in industrial pharmacy department at Pharmacy School of University of Tripoli. She gave lectures and run lab works. She has received another funding from her the University on 2013 under Libyan grant agreement of 293/2013. In Jan 2015 she joined the University of Manchester for a PhD in Pharmaceutical sciences. Her role as PhD student is to conduct research to evaluate and improve stability of a protein called rhIL-1Ra. Find out root causes of instability of rhIL-1Ra. Conduct several pre-formulation studies by using different biophysical techniques such as Static and Dynamic Light Scattering (OD,DLS), Circular Dichroism (CD), Differential Scanning Colorimeter DSC and SDS-Electrophoresis. Find a new formulation technique to address stability problem of the protein. Currently, she is also work as teaching assistant (demonstrator) at University of Manchester.

Design and synthesis of new EF2K inhibitors for the treatment of TNBC and pancreatic cancers and their in vitro release studies from biocompatible natural polymeric particles

Ferah Cömert Önder^{a*} (PhD Student), Selin Sagbas^b (PhD Student), Mehmet Ay^a (PhD), Tuğba Taşkın Tok^c (PhD), Bülent Özpolat^d (PhD), Nurettin Sahiner^b (PhD), Esen Bellur Atici^c (PhD), Bekir Karlığa^c (PhD)

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Triple-negative breast cancer (TNBC) and pancreatic cancers are aggressive malignancies that respond poorly to treatments and is associated with high rates patient deaths despite surgery and adjuvant chemotherapy. With the currently available chemotherapeutics 5-survival rates of TNBC is 30 % and pancreatic cancer 1-2 % (with median survival only 6 months). Thus, identification of common and clinically significant molecular targets would help developing targeted therapies for these patients. Recently, potent EF2K inhibitors were tested in vitro and in vivo (mice models) of TNBC and panc cancer models using siRNA or microRNA based gene silencing strategy. There is clearly an urgent need to identify better eEF2K inhibitors to target in various cancers. For this purpose, we designed potent new EF2K inhibitors using computational chemistry techniques and synthesized substituted chromenecarboxamide derivatives were confirmed by melting point, FT-IR, ¹H-NMR, ¹³C-NMR, LC-MS spectral analysis. Furthermore, in vitro release studies of these inhibitors were carried out from biocompatible microgels particles with different size ranges (50 nm -500 µm) that prepared from natural polymers such as hyaluronic acid and/or and polymeric sucrose particles.

Identification of EF2K inhibitors may have tremendous impact in the treatment of TNBC, and panc cancer and can be translated into clinic.

Takeaway Notes:

- Highlight the importance of protein kinases in the cancer therapy.
- How to design potent new inhibitors and approach to their synthesis and using of drug delivery systems.
- Design new projects with collaboration for cancer therapy.

Biography

Mrs. Cömert Önder graduated as BSc&MSc in Chemistry in 2012 and PhD is still continuing at Science Faculty, Çanakkale Onsekiz Mart University under Supervision of Dr. Mehmet AY. Experienced 3 months Lab. training at Wolverhampton University in UK, 2011. She is going on research activities in Dr AY's Natural Products and Drug Research Lab., focusing on developing new prodrug and drug molecules for Cancer Therapy.

Method indicative of stability for determination of rifaximin and its degradation products by thin chromatographic

Dr. Ana Carolina Kogawa^{1*}, Dr. Jacqueline Nakau Mendonça², Prof. Dr. Norberto Peporine Lopes², Prof. Dr. Hérica Regina Nunes Salgado¹

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Rifaximin is an oral antimicrobial, intestine-selective and non systemic with adverse effects compared to placebo. Rifaximin, until then, does not have standardized analytical methods in most official compendia. Fast, economic, environmentally friendly and selective method indicative of stability by thin chromatographic (TC) for the determination of rifaximin and its degradation products was designed. The TC method used silica gel as stationary phase and ethyl acetate: ethyl alcohol, 90:10 (v/v), as mobile phase to achieve spots for rifaximin ($R_f=0.62$) and its degradation products basic ($R_f=0.33, 0.49, 0.56$), acidic ($R_f=0.47, 0.54$), oxidative ($R_f=0.28$) and neutral ($R_f=0.32$). The plates were visualized in chamber UV at 254 nm. Simultaneously, analysis of high performance liquid chromatography (HPLC) was performed using Eclipse Plus C18 (150 mm x 4.6 mm) column and purified water + 0.1 % glacial acetic acid and ethanol in the ratio 52:48 (v/v) as mobile phase at 290 nm. The objective was to verify the interchangeability of TLC and HPLC methods in obtaining the degradation products of rifaximin tablets. In HPLC, as in TLC was observed the rifaximin (RT=5.5) and its degradation products acidic, basic (RT =4.2 and 4.7), oxidative (RT =3.6 min) and neutral (RT =4.7 min). These techniques can be used as methods indicative of stability, because they identify the rifaximin and their degradation products. Therefore they can be effectively applied in quality control of rifaximin in tablets. The study of alternative methods should be encouraged by reducing costs, allowing the use of environmentally friendly solvents, optimize analysts and equipment while providing quality analyzes.

Takeaway Notes:

- TLC method for determination of rifaximin and its degradation products was developed.
- The investigation of alternative methods such as this should be valued.
- It helps reduce costs, allows the use of environmentally friendly solvents.
- Moreover, it optimizes analysts and equipment while providing quality analyzes.

Biography

Ana Carolina Kogawa graduated in Pharmacy-Biochemistry (2008), Master (2012) and PhD in Pharmaceutical Sciences (2015) from "Universidade Estadual Paulista – UNESP" (Brazil). She has experience in managing people, lectures, quality tools and pharmaceuticals activities of industry with emphasis on Quality Control. Currently she conducts a project financed by Fundação de Amparo à Pesquisa do Estado de São Paulo (Fapesp) with the drug rifaximin for the development of her Postdoctoral research at the School of Pharmaceutical Sciences of Araraquara, Brazil.

Comparison of UV, IR, CE, HPLC and turbidimetric methods in the evaluation of rifaximin

Dr. Ana Carolina Kogawa*, Prof. Dr. Hérica Regina Nunes Salgado

School of Pharmaceutical Sciences of Araraquara, Univ Estadual Paulista – UNESP, Brazil

An adequate analytical method can be the first step in the rational use of pharmaceuticals. Currently, however, the effectiveness of the method of analysis is not enough. It should also be environmentally friendly, dynamic and low cost. A product can present more than one analytical method for its evaluation, and then, before adopting any of them, it is necessary to know if they are equivalent. Comparison of methodologies is necessary to determine if the variability of the methods differs significantly. Rifaximin, an antimicrobial, presents analytical methods by spectrophotometry in the ultraviolet region (UV), spectrophotometry in the infrared region (IR), capillary electrophoresis (CE), high performance liquid chromatography (HPLC) and Turbidimetry for evaluation of its tablets. This work shows the comparison of these methods in the evaluation of the final product quality of rifaximin, in addition to comparing the equivalence of physical (UV, IR, CE, HPLC) and microbiological (Turbidimetric) methods. The analysis of rifaximin tablets by physico-chemical and microbiological methods were statistically equivalent and can be interchangeable. However, it should be remembered that in the case of antimicrobials, such as rifaximin, the simultaneous analysis by a physico-chemical method and a microbiological method is fundamental for the release of reliable results.

Takeaway Notes:

- Analytical methods can be the first step in the rational use of pharmaceuticals.
- Comparison of methodologies determines if the variability of the methods differs significantly.
- The analysis of rifaximin tablets by physico-chemical and microbiological methods were statistically equivalent and can be interchangeable.

Biography

Ana Carolina Kogawa graduated in Pharmacy-Biochemistry (2008), Master (2012) and PhD in Pharmaceutical Sciences (2015) from "Universidade Estadual Paulista – UNESP" (Brazil). She has experience in managing people, lectures, quality tools and pharmaceuticals activities of industry with emphasis on Quality Control. Currently she conducts a project financed by Fundação de Amparo à Pesquisa do Estado de São Paulo with the drug rifaximin for the development of her Postdoctoral research at the School of Pharmaceutical Sciences of Araraquara, Brazil.

Polyphenols loaded vaginal microbicide: A novel strategy for prevention of HIV transmission

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²Department of Biochemistry, National Institute for Research in Reproductive Health, Parel, Mumbai, Maharashtra, India

The unprotected sexual intercourse associated HIV is one of the most serious challenges to public health all over the world. According to recent reports, sexual transmission is the predominant mode of HIV transmission. This rate could be declined by a prophylactic strategy using a microbicide. Several prophylactic microbicides, when tested clinically, have failed to show efficacy and exert poor adherence which is mainly attributed to the emergence of drug resistance, severe adverse effects. Thus, there is a need for identification of safe and effective drug candidates that can prevent early stage transmission HIV-1 via unprotected sexual intercourse. Polyphenols are the naturally occurring secondary metabolites with wide therapeutic activities viz., anti-viral, anti-cancer, anti-aging, etc. However, the polyphenols which act at early stage gp120-CD4 binding inhibition are not yet identified. With this understanding, a suitable class of naturally occurring polyphenols was subjected to in silico screening (molecular docking and dynamics simulation studies) using homology model of gp12-CD4 binding. Amongst the tested polyphenols, punicalagin exhibited superior gp120-CD4 binding affinity due to its stable hydrophobic interactions with residues Asp368 and Trp427 at deeper site in the Phe43 cavity and the same was confirmed by in vitro cell line study ($IC_{50} = 0.237 \mu M$) and hence it was considered as a lead. With this proof, Punicalagin rich *P. granatum* extract loaded novel microbicide gel was developed and optimised for efficient delivery via the rectal/vaginal route. The *P. granatum* extract loaded nanomicrobicide gel exhibited 40 times higher anti HIV activity as compared to tenofovir disoproxil fumarate. Further, it showed mild but acceptable irritation score when tested in rabbits for consecutive 14 days application. Thus, the novel natural nanomicrobicide ensured enhanced efficacy and acceptable safety proving the potential of polyphenols as gp120-CD4 binding inhibitors for prevention of HIV transmission via unprotected sexual intercourse.

Takeaway Notes:

- HIV prophylaxis is a niche area where the research still is in clinical phase. The lack of effective formulation strategy is the major concern for the success of HIV prophylaxis. The proposed work would help the audience to understand the role of key excipients with inherent therapeutic effect and herbal entities to provide complete HIV-1 prophylaxis
- The proposed nanotechnology could be utilised for different hydrophilic/lipophilic entities for both vaginal/rectal delivery
- Encourage the audience to adapt reverse pharmacology for life-threatening diseases.

Biography

Amit is a Senior Research Fellow pursuing his Ph.D. (Tech.) degree in Pharmaceutics with Prof. Vandana B. Patravale in Department of Pharmaceutical Sciences and Technology at Institute of Chemical Technology (ICT), Mumbai. Amit is currently working on "Nanotherapeutics for Prophylaxis of HIV" sponsored by DBT-ICMR agency. He has 2 international publications and has co-authored 3 book chapters in "Pharmaceutical Product Development" published by Taylor & Francis Inc. He has also won 3 Best Poster Awards in International Conferences.

Nanoparticle Engineering of atovaquone using nano-by-design (NbD) approach

Pratik S. Kakade* (Senior research fellow), Sandip M. Gite (Senior research fellow); Vandana B. Patravale (Ph.D.)
Institute of chemical technology, Mumbai, India.

One of the major problems of poorly soluble drugs is low bioavailability. The problem is basically related with BCS class II drugs which are poorly soluble in both aqueous and nonaqueous media. Atovaquone (ATQ), a BCS class II molecule is primarily used to treat or prevent pneumonia caused by a fungal infection called *Pneumocystis carinii* (also called *Pneumocystis jirovecii*). Atovaquone (ATQ) is a highly lipophilic molecule ($\log P = 5.31$) and practically insoluble in 0.1 N HCl and water. Further, it has a pKa of 9.1, rendering it essentially neutral under the pH of physiological conditions. This has resulted in its poor and unreliable absorption. Mean absolute bioavailability of ATQ is 21%.

The aim of the present study was the development of nanosuspension of ATQ using Nano by design (NbD) approach to overcome bioavailability related issues associated with the drug. Microfluidization and High-pressure homogenization (HPH) techniques were used for the processing the formulation. The patient-centric quality target product profile (QTPP) and critical quality attributes (CQAs) were earmarked. Critical formulation parameters (CFPs) such as drug: stabilizer ratio and critical process parameters (CPPs) like number of cycles and pressure were identified as high impact parameters affecting particle size and polydispersibility index in risk assessment studies in both the techniques. A Box Benhken design (BBD) was employed for optimization. The design spaces were generated, and the optimum formulations were located using desirability parameters, followed by its validation. Further, the prepared nanosuspensions were characterized for the DSC, FTIR, XRD, In-vitro dissolution studies etc. The results were compared to pinpoint merits and demerits of both the techniques.

Takeaway Notes:

- The audience will learn two techniques of nanoformulations viz. high pressure homogenization and microfluidic homogenization as well as the regulatory perspective of using Nano-by-design approach.
- Other faculty could use the technology for BCS class II and IV drugs.
- The technology could be used to decrease the dose and dosage frequency of the developed dosage form.

Biography

Pratik S. Kakade is senior research fellow perusing Ph.D. (Tech) degree in Department of Pharmaceutical Sciences and Technology at Institute of Chemical Technology, Mumbai, India. He has 3 International publications to his credit. He has participated in various National and International forums as an Oral/Poster presenter and won awards. He has successfully completed industrial M. Pharm and a project on Herbal solid oral dosage form sponsored by an Industry. He was bestowed 'Best outgoing student award' by his alma mater.

Analytical method development and validation of End-LAA for in vitro and in vivo studies.

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Endomorphin-1 is more effective in the treatment of neuropathic pain than morphine-like analgesics and side effects after treatment are less due to its endogenous nature. However, endomorphin-1 cannot be clinically used for reasons such as short duration of action, poor metabolic stability, vaginal bleeding, and failure to pass through the blood-brain barrier. Therefore lipid-modified derivate of endomorphin-1 peptide (End-LAA) was prepared to provide its oral bioavailability. Current study comprises the analytical method development and validation to determine End-LAA amount in in vitro studies and in vivo biological samples.

Liquid chromatography–mass/mass spectrometry (LC-MS/MS) method was developed using ACE C18 (50mm x 4.6 mm x 5µm) column with a flow rate of 0.5 mL/min. End-LAA level measurement was performed by electrospray ionization (ESI) method and positive ion mode using an Agilent 6420 LC-MS / MS instrument. The mobile phase was consisted of 0.1% v/v formic acid solution in acetonitrile and 0.1% v/v formic acid solution in water. The main mass/charge (m/z) value of End-LAA was 780.3, and the Q3 m/z values obtained therefrom were 448.3 and 284.1. The fragmentor voltage was applied as 160 V. Standard solutions of End-LAA in acetonitrile and plasma were prepared within a concentration range of 0.19- 100 ng/mL. The calibration curves were obtained with R² values of 0.995 -0.998. The proposed method was extensively validated in terms of precision, accuracy, linearity and range. Besides, the limit of detection and quantification values were also calculated and discussed according to Guidelines.

As a result a simple, selective and rapid LC–MS/MS method has been developed and validated for the sensitive determination of End-LAA.

The authors wish to thank Prof. Dr Istvan Toth (University of Queensland, Australlia) for synthesis and providing of End-LAA.

Biography

Cansel Kose Ozkan was born in Izmir-Karsiyaka in 1976 and completed her undergraduate education at Gazi University Faculty of Pharmacy in 1997. In 1999, she joined the Turkish Naval Forces as an active pharmacist officer. She completed her master's degree in Gulhane Military Medical Academy Center of Pharmaceutical Sciences in 2003 and in 2007 completed PhD degree at the same institution. She worked as a member of the Inspection and Acceptance Commission in the Ministry of Defence between 2007-2009. In 2010, she was appointed as Assistant Professor at Gulhane Military Medical Academy Center of Pharmaceutical Sciences Department of Pharmaceutical Technology. Since 2016, she is a part-time teaching staff at the Center of Pharmaceutical Sciences of the University of Health Sciences. She also work in the Ministry of Health Hospital Pharmacy Management Unit. I know English and German.

DAY 3

Keynote Forum

Global Conference on
**Pharmaceuticals and
Drug Delivery Systems**

June 29 - July 01, 2017 | Valencia, Spain

PDDS 2017

Nanocomposite microparticles for the pulmonary delivery of bio-macromolecules

G.A. Hutcheon *Ph.D*

Liverpool John Moores University, UK



The development of new biopharmaceutical therapeutics including proteins, peptides, vaccines, antibodies and nucleic acids is steadily increasing presenting new opportunities for the treatment and prevention of disease. However, it is challenging to effectively deliver these biomacromolecules and the oral route has the disadvantage of the harsh stomach environment that results in degradation. By comparison, the pulmonary route offers several advantages for both local and systemic delivery such as; a large surface area, a thin epithelium, dense vasculature, less enzymatic activity and is non-invasive. Various polymers have been investigated for the particulate delivery of macromolecules providing increased stability, sustained release and the potential for targeted delivery; the most common being Poly lactic-co-glycolic acid (PLGA). Nanoparticles (NPs) have shown potential for the delivery of macromolecules to tissues and cells but are too small to be deposited in the lung via inhalation. They can be incorporated into nanocomposite microcarriers (NMC) for dry powder inhalation (DPI).

As an alternative to PLGA we have utilised poly(glycerol adipate-co- ω -pentadecalactone), PGA-co-PDL, to prepare NPs followed by spray drying to produce NCMPs suitable for dry powder inhalation. The properties of both NPs and NCMPs were optimized for different applications using Taguchi's design of experiment and loaded with, for example; proteolytic enzymes, pneumococcal vaccine and miRNA.

NPs were prepared using an oil-in-water single emulsion solvent evaporation method followed by adsorption of the biomacromolecule from solution or the biomacromolecules were directly encapsulated using a double oil-in-water-in-oil method. NPs were characterised in terms of size, charge and drug loading and then spray-dried in an aqueous suspension of L-leucine (1:1.5) using a Büchi-290 mini-spray dryer. The resultant NCMPs were characterised for toxicity, aerosolization, in vitro release study, stability and activity.

Typically, NPs with adsorbed protein were of between 120 and 150nm in size and with encapsulated protein were around 200-220nm; both suitable for targeting lung cells. Typically, 10-20 μ g of a model protein (BSA) was adsorbed per mg of NPs and 40 μ g/mg was encapsulated, dependant on the conditions used. Spray-drying with L-leucine resulted in a 50% yield of NCMPs with a fine particle fraction (FPF%) $d_{ae} < 4.46 \mu$ m of around 75% and a mass median aerodynamic diameter (MMAD) of 1-3 μ m suggesting deposition will be in the broncho-alveolar region of the lung. Cell viability was typically between 70-85% (A549 cell line) at 1.25 mg/ml concentration after 24 h treatment. SDS-PAGE and CD confirmed the primary and secondary structure of the released BSA was mainly conserved.

For the pneumococcal surface protein A (PspA) study, the activity of the PspA vaccine was confirmed using the lactoferrin binding assay. Similarly, internalization of mi-146A loaded cationic NPs to treat COPD was observed in adenocarcinomic human alveolar basal epithelial and alveoli cell lines using confocal microscopy. The miR146a delivered had a dose dependent effect on target gene repression (IRAK1). These examples demonstrate the potential of PGA-co-PDL NPs as a pulmonary delivery system for vaccination and to treat lung disease.

Takeaway Notes

During this talk the following information will be provided

Global Conference on

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- The synthesis, modification and application of a new polymer, PGA-co-PDL for drug delivery
- A technique for the encapsulation or adsorption of biomacromolecules onto polymeric NPs
- A technique for the incorporation of the NPs into a microcarrier for pulmonary delivery
- Examples of applications of this delivery system
- This NCMP drug delivery system can potentially be utilized for the delivery of a variety of biomacromolecules and small drug molecules via DPI either to the lung or potentially via the nasal route. We are happy to collaborate on such projects using this technology for alternative applications.

Biography

Gillian Hutcheon graduated from Strathclyde University, Scotland in 1996 with a PhD thesis on Biocatalysts in non-aqueous media. She then undertook postdoctoral research at Queens Medical Centre, Nottingham investigating Protein: Biomaterial interactions. She joined Liverpool John Moores University in 1999 as a lecturer in Organic Chemistry and leads the Formulation and Drug Delivery Research Group. She has evolved her interest in proteins and biomaterials towards drug delivery applications looking at the enzyme catalysed synthesis of novel materials for micro and nanoparticle delivery of small molecule drugs and biomolecules. In 2008 she was conferred as a Reader in Biomaterials and she is currently Head of the LJMU Institute for Health Research.

Development of nitroreductase/prodrug system for cancer therapy

Mehmet Ay *Ph.D*

Çanakkale Onsekiz Mart University, Turkey



Conversion of an inactive drug (prodrug) into an active drug is the starting point of the Enzyme Prodrug Therapy (EPT), one of the novel strategies attracted attention increasingly over 20 years to develop new solutions for various illness. Nitroreductases reduce aromatic nitro groups and convert prodrugs to hydroxylamine derivatives (active drug) which can bind to DNA and inhibit tumor formation. The best known example in the enzyme mediated cancer therapy is probably the use of E.coli NTR in combination with the prodrug CB1954 (5-aziridinyl-2-4-dinitrobenzamide). In this study, first of all, we explored and characterized a novel nitroreductase (Ssap-NtrB-cloned from *S. saprophyticus*) with enhanced activity-selectivity and implemented various applications. Different type of nitro group containing compounds were designed, synthesized and the interaction of prodrugs with Ssap-NtrB were investigated by HPLC analysis. Resulting metabolites were analyzed by LC-MS/MS. Michaelis-Menten kinetic parameters were calculated for reduction reactions of prodrugs and compared common known prodrugs like as CB1954 and SN23862. The prodrugs were evaluated by MTT and SRB assay in three different cancer cell lines, Human Hepatoma Cancer (Hep3B), Human Colon Cancer (HT-29) and Human Prostate Cancer (PC3) in addition to non-cancer cell, HUVEC.

Promising results along this side are going to be discussed.

Takeaway Notes

- How to use prodrug approach for expanding their research or teaching,
- Realize importance of nitroreductase to drug design and other applications,
- Design new projects with collaboration for cancer therapy.

Biography

Dr. Mehmet Ay graduated as BSc&MSc in Chemical Engineering in 1980 and PhD in 1989 at Science Faculty, Ankara University under Supervision of Dr. Ender Erdik. Experienced 6 months Lab. training at Würzburg University in AKS. Hünig, 1980-1981, Germany; 16 months Post Doctoral Research Assoc. at Purdue University in Dr. E. NEGISHI's lab, W. Lafayette, 1991-1993, USA. Since 1999 as a Faculty at Çanakkale Onsekiz Mart University, Department of Chemistry is going on teaching and research activities in his Natural Products and Drug Research Lab., focusing on developing new prodrug and drug molecules for Cancer Therapy.

Pharmaceutics and Drug Delivery Systems

June 29 - July 01, 2017
Valencia, Spain

Why perform pharmaceutical analysis green and optimized?

Ana Carolina Kogawa *Ph.D*

Univ Estadual Paulista - UNESP, Brazil



Because we should think that everything is interconnected and we are part of a system. Pharmaceutical analyzes are an item in the sciences and, as all of them, should act consciously in the world. Have you ever thought about the social, environmental and economic impact of your analytical decisions?

Pharmaceutical analyzes by spectrophotometry in the ultraviolet and visible region using water as solvent system, high performance liquid chromatography using only ethanol and water in the mobile phase, spectrophotometry in the infrared region using only potassium bromide as reagent, thin layer chromatography for evaluation of degradation products and turbidimetry for microbiological evaluation of antibiotics are examples of green or clean methods.

Another important characteristic to be highlighted is the optimization of time and analysts which this type of methodology provides. They are fast methods which provide extra time to energize a process and analyst to other activities.

Fast, low cost, easy to run, which uses non-toxic reagents for the operator and for the environment, without waste of intellect and robust are the characteristics of a modern and current pharmaceutical analysis.

Changing standards is difficult, therefore the courage and persistence are so valued. Methods with socio-economic-environmental concerns should be shouted to the world.

Biography

Ana Carolina Kogawa graduated in Pharmacy-Biochemistry (2008), Master (2012) and PhD in Pharmaceutical Sciences (2015) from "Universidade Estadual Paulista – UNESP" (Brazil). She has experience in managing people, lectures, quality tools and pharmaceuticals activities of industry with emphasis on Quality Control. Currently she conducts a project financed by Fundação de Amparo à Pesquisa do Estado de São Paulo with the drug rifaximin for the development of her Postdoctoral research at the School of Pharmaceutical Sciences of Araraquara, Brazil.

PDDS 2017

DAY 3

Speakers

Global Conference on
**Pharmaceuticals and
Drug Delivery Systems**

June 29 - July 01, 2017 | Valencia, Spain

PDDS 2017

Session on: Biodrugs, Biomolecules and Therapeutics | Pharmaceutical Research | Therapeutic Drug Carrier Systems

Session Chairs

Gillian Hutcheon

Liverpool John Moores University, UK

Ulo Langel

Stockholm University, Sweden

Session Introduction

Title: Impact of drug crystal habit on drug-carrier surface interactions and consequent powder dispersion from dry powder inhalers

M. Teresa Carvajal, Purdue University West Lafayette, USA

Title: INN Darunavir. Patenting problem of active pharmaceutical substances

Mikhail Samuilovich Goizman, Drugs Technology LLC, Russia

Title: Preclinical development of GMC1, a novel molecule targeting FKBP52 for the treatment of castration resistance prostate cancer

Huan Xie, Texas Southern University, USA

Title: Development of formulations for novel chemotherapeutic agents for Tuberculosis and HIV co-infection

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Title: Steroid estrogen analogues as potential drugs with targeted action

Svetlana N. Morozkina, ITMO University, Russia

Title: The bone-cartilage interface: A complex biological barrier with potential therapeutical targets

Elod Erno Nagy, University of Medicine and Pharmacy Targu-Mures, Romania

Title: Improvements of computational optimization of drug-target interactions

Csaba Hetenyi, University of Pecs, Hungary

Title: Towards improved activity and stability of gene therapeutics

Kira Astakhova, University of Southern Denmark, Denmark

Title: Smart lipid nanocarriers: Potential for intracellular targeting

Vandana B. Patravale, Institute of Chemical Technology, India

Title: Potentiation of cytotoxic action of the new cisplatin derivative by UV irradiation

Jitka Pracharova, Palacky University, Czech Republic

Title: Impact of gut microbiota-mediated bile acid metabolism on the solubilization capacity of bile salt micelles and drug biopharmaceutical properties

Elaine F. Enright, University College Cork, Ireland

Title: Development of intravenous form of rifapentine and its in vivo evaluation

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Title: Green technology approach for development of BCS Class II molecule nanoformulation

Sandip Gite, Institute of Chemical Technology, India

Impact of drug crystal habit on drug-carrier surface interactions and consequent powder dispersion from dry powder inhalers

M. Teresa Carvajal

Purdue University West Lafayette, USA

The physicochemical properties of drug particles from two polymorphs were studied in terms of their observable effects on the nature and strength of the interactive forces between drug particles from different polymorphs and lactose in dry powder mixes for inhalation. The type of systems was chosen to investigate the interactive properties of two different surfaces of the same chemical composition. The hypothesis was that the two polymorphs of the same drug would exhibit measurable differences in their inter-particle cohesive/adhesive interactions. These manifest themselves macroscopically by having different ease of metering and in powder dispersion, that in turn at the molecular level are the result of surface energetics of the two polymorphs. The results of the surface energy properties of the two polymorphs revealed that polymorph A elongated crystal habit exhibited stronger cohesive and adhesive interactions than its counterpart polymorph B rounded. In addition, the results also suggest that the effects of surface geometry of the drug particles continues to play a significant, although not necessarily dominant role in the aerosol dispersion and deposition properties of the powder mixes.

Biography

Teresa Carvajal is a faculty member of the Agricultural and Biological Engineering department at Purdue University. Dr. Carvajal's research focuses on surface science to assess issues and behavior of powders as a result of the inherent solid state structural, physicochemical, particle surface (interactions e.g. adhesion/cohesion and electrostatics) and mechanical properties. The effects of these properties on powder agglomeration, dispersion and flow could be detrimental on the final pharmaceutical product. Her research interests are on probing surface and bulk properties at the microscopic level to be able to manipulate their characteristics at the macroscopic level and get involved in strategies for controlling behavior of powders. Her experimental approach is to use various techniques thermal, spectroscopic and surface characterization to interrogate materials. Her work on fundamental understanding of the systems extends to design, control and choose appropriate materials for formulation development of powders for inhalation and beverage.

Prior to joining Purdue University, Dr. Carvajal worked in the pharmaceutical industry for 13 years. She worked at Hoffmann-LaRoche (Nutley, NJ) in the area of oral dosage form development. Working on the behavior of powders and powder blends, her activities expanded to research and development of formulations for pulmonary delivery of small molecules and peptides. She later joined Bayer Pharmaceuticals (West Haven, CT) where she was responsible for pre-formulation activities as well as early formulation development for lead compounds of drug discovery. She has been an invited and keynote speaker at various national and international conferences. Dr. Carvajal gives short courses to industry on a various topics in Powder Technology to the USA, Europe and Latin America.

INN Darunavir. Patenting problem of active pharmaceutical substances

M.S. Goizman* Ph.D., L.V. Akobyan Ph.D., D.L. Shobolov Ph.D., O.A. Zotova Ph.D., N.L. Shimanovsky Ph.D., A.A. Korlyukov Ph.D., K.Yu. Suponitsky Ph.D.
Drugs Technology LLC, Russia

One of the best HIV-protease inhibitors is [(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol](1S,2R)-3-[[[(4-aminophenyl)sulphonyl] (isobutyl) amino]-1-benzyl-2-hydroxypropyl]carbamate (I) (INN Darunavir). PREZISTA and KEMERUVIR drugs contain Darunavir active pharmaceutical ingredient (API): the first one – in the form of crystalline ethanolate, the second one in the amorphous form. As HIV-protease inhibitor, compound I, its chemical structure and production process were at first time described in the patent “Hydroxyethylaminosulphonamides useful as retroviral protease inhibitors”, which has been enjoying conventional priority since August 24, 1993. INN Darunavir was suggested to honor prof. Arun K. Ghosh, the author of the research work. The production process for Darunavir amorphous using its ethanolate was described 16 years later in the patent “Polymorphs of darunavir”, which has been enjoying conventional priority since January 29, 2009. With due regard to the patents, the date when clinical studies of compound I (i.e. DRV) under code name of TMC 114 began, and the decision by FDA USP dated June 23, 2006 authorizing the use of PREZISTA® tablets, containing specifically Darunavirethanolate as their API, it must be acknowledged that it has been de-facto used as API since 2001. The dosage of PREZISTA® tablets is indicated in equivalent of compound I (INN Darunavir). Despite publication of the work, Tibotec Pharmaceuticals Ltd. filed a patent application on May 16, 2002, No 02076929.5, with a title containing undefined information: “Pseudopolymorphic forms of a HIV protease inhibitor”.

The application described compound I as HIV protease inhibitor under its chemical name and without the indication of INN, which allowed, without focusing on the lack of novelty, to claim as subject of patenting a number of solvates (pseudopolymorphs) of compound I allegedly derived from its amorphous form. Among others, the ethanolate of compound I was claimed, while its clinical tests had been started back in 2001. Then, Tibotec Pharmaceuticals Ltd. filed the application No. PCT/EP2003/050176, according to which parallel patents were issued with conventional priority dated 16.05.02. The article shows that the above patents containing false information, chemical and terminological errors have no right to exist. It is obvious that the applicants neglected the requirements of ethics, because they attempted to illegally monopolize the production of vitally important API, i.e. DRV ethanolate.

Takeaway Notes:

The paper deals with specific difficulties associated with attempts to reuse patented API. It shows that re-patented work API with INN Darunavir performed in violation of ethical standards. In addition, the patent authors were allowed chemical and terminological mistakes, indicating the lack of qualifications of the authors. This report is a useful example, demonstrating a principled approach to assessing attempts at secondary patenting of APIs, for the purpose of monopolizing their production and use.

Biography

Mikhail Samuilovich Goizman was born in Moscow, in 1939. In 1961 he graduated from the Moscow Chemical Technology Institute “MHTI” (now Dmitry Mendeleev University of Chemical Technology) specializing in the technology of petrochemical synthesis, from 1965 to 1998 worked in the All-Russian Scientific Research Chemical-Pharmaceutical Institute. The author of a number of General Pharmacopeia monographs in the State Pharmacopoeia of the USSR and Russia. At present Deputy General Director of “Drugs Technology” LLC. In 1972 defended the dissertation “Thermocatalytic titration of bases in a medium of protogenic solvents”, Ph. D., Laureate of State Prize “Council of Ministers of the USSR”.

Area of scientific interests: analytical chemistry, synthesis and quality control of APIs. Ethical problems of patenting in the field of pharmacy.

Preclinical development of GMC1, a novel molecule targeting FKBP52 for the treatment of castration resistance prostate cancer

Oscar Ekpenyong¹, Ph.D. candidate; Marc Cox², Ph.D.; Jaideep Chaudhary³, Ph.D.; Huan Xie¹, Ph.D.

¹Texas Southern University, USA

²The University of Texas at El Paso, USA

³Clark Atlanta University, USA

Purpose: GMC1 directly inhibits FKBP52, effectively blocking androgen receptor dependent gene expression and androgen-stimulated proliferation. This makes it an attractive option for the treatment of hormone-dependent and hormone-independent prostate cancer. This study investigated an analytical method for GMC1 quantification, pre-formulation characteristics of GMC1, and developed intravenous formulations for the evaluation of GMC1 in animal models.

Method: An LC/MS/MS method for the quantification of GMC1 in solution, plasma and urine was developed, validated and applied to the determination of the stability, log P, plasma protein binding and solubility of GMC1 in various solvents. Liposomal formulations and co-solvent systems with various ratios of high capacity vehicles were formulated and the optimal formulation applied, at 2 mg/kg single IV bolus dose, to the pharmacokinetic study of GMC1 in a rat model. In vivo efficacy study has been performed on xenograft mouse model

Result: The intra- and inter-day accuracy (%RE) and precision (%CV) of the LC/MS/MS method ranged from 1.6 – 11.7 % and 1.4 – 8.8 %, respectively. GMC1 is stable in solid and solution state, moderately lipophilic ($\log P = 1.38 \pm 0.05$), poorly water soluble (0.4 ± 0.01 mg/mL), and highly plasma protein bound (>71%). The optimal formulation consisting of PEG 300 and Labrasol[®] (1:1, v/v) allowed us to achieve a GMC1 concentration of 10 mg/mL, and tolerated an aqueous environment. GMC1 has a tri-exponential disposition with a C_{max} of 7.6 ± 1.97 mg/L, clearance of 0.53 L/kg/hr, α -distribution, β -phase and terminal elimination half-lives of 0.1 ± 0.04 hr, 1.2 ± 0.34 hr, and 19.7 ± 5.09 hr respectively. The in vivo efficacy study in nude mice with LNCaP-ID4 xenograft showed significant tumor inhibition in the GMC1 treated group compared with the control group.

Conclusion: The LC/MS/MS method, formulations, pharmacokinetics and efficacy study can be applied to the clinical development of GMC1.

Takeaway Notes:

- This project shows a well-designed preclinical development of a novel first-in-class drug for castration resistant prostate cancer, a deadly disease.
- Other faculty could use this project as an example to design their research or teach the student the essential components for a preclinical study.
- It can provide a practical solution to help a designer on solving seminar formulation study of other drugs.
- It can provide new information to assist in design a preclinical study for other drugs.

Biography

Dr. Huan Xie has a broad background in nano-formulation, drug delivery and pharmacokinetics, with specific focus and expertise in cancer therapy applications. She had 4-year industrial working experience contributing the development of novel nanoshells for photothermal ablation cancer therapy. At Texas Southern University, she has been focused on novel drug preclinical development. Now she is Director of TSU Pharmacology Core with track record of publications, NIH grant support and patent applications.

Development of formulations for novel chemotherapeutic agents for Tuberculosis and HIV co-infection.

Omonike A. Olaleye, Ph.D.^{1*}, Sarah F. John, Ph.D.², Fadia Boughaba¹, Lyndsey White, Ph.D.³ and Dong Liang, Ph.D.¹

¹Texas Southern University, USA

²University of St. Thomas, USA

³Charles River Laboratory, USA

Background: Human immunodeficiency virus (HIV) has changed the global profile of Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB). TB is the leading cause of death in AIDS patients worldwide. The apparent lethal synergy of TB with HIV has made the requirement for the development of new anti-TB and anti-HIV agents more imperative. Presently, the therapeutic management of HIV patients co-infected with Mtb poses great challenges because of drug-drug interactions and toxicity. Moreover, the emergence of multidrug resistant TB (MDR-TB) in HIV patients threatens to put an end to the efficacy of these drugs. Therapy for MDR-TB takes several years to complete, comprises of toxic second line drugs, and has high failure rates. Therefore, novel ways to treat HIV patients co-infected with TB are needed. Our research efforts have been focused on the development of formulations for new therapeutic agents for treatment of both TB and HIV infection. Our hypothesis is that therapeutically targeting TB and HIV with our novel inhibitors will treat and/or limit the progression and dissemination of these pathogens in co-infected patients.

Methods: While at the Johns Hopkins University School of Medicine, Dr. OmonikeOlaleye used a spectrophotometric assay to screen a library of 175,000 structurally diverse small molecules and identified novel potent inhibitors of M. tuberculosis. Following this analysis, we determined the potency of these inhibitors on HIV infectivity and developed a novel assay for the high-throughput screening (HTS) of inhibitors. Thereafter, we developed formulations for three new anti-TB-HIV chemotherapeutic agents.

Results: We characterized and developed formulations for potent novel compounds that have dual anti-TB and anti-HIV activity with safe pharmacologic profiles. The preliminary pharmacokinetic and cytotoxicity studies have shown promising results for the newly discovered compounds. Our results with the novel HTS assay has demonstrated the utility of this model to rapidly evaluate drug effectiveness relevant to cellular toxicity, HIV-1 replication, and intracellular mycobacterial growth.

Conclusion: The clinical significance of this study is that: The therapeutic targeting of TB-HIV activity in co-infected patients would accelerate the future development of new agents to treat drug-resistant TB and HIV infections in the clinic. Moreover, the development of a new formulation has great value in accelerating the discovery of new compounds for use in TB/HIV co-infected patients. Our results provide critical data with direct implications on efforts to control the global HIV and TB pandemics.

Takeaway Notes:

- The development of pre-formulations and formulations for these inhibitors against TB and HIV.
- The development of formulations for these inhibitors against TB and HIV.
- The development of a novel HTS assay for new small molecules targeting TB and HIV.

Biography

Omonike Arike Olaleye, Ph.D. is an Associate Professor of Pharmacology in the College of Pharmacy and Health Sciences (COPHS) at Texas Southern University (TSU). She has over 16 years of research experience in drug discovery and development in major pharmaceutical companies and academia. Her formal training in pharmacology was at the Johns Hopkins University School of Medicine (JHU), Baltimore, Maryland. At JHU, she was awarded prestigious pre-doctoral fellowships from both National Aeronautics Space Administration (NASA) and Merck Research Laboratories. Recently, her work has been on the development of new therapeutic agents and formulations for treatment of drug resistant TB and HIV co-infection. She has characterized potential drug candidates for chemotherapy of TB and HIV co-infection. Dr. Olaleye has received several extramural funds and established productive collaborations resulting in awarded grants, publications and patents. In 2016, Dr. Olaleye was awarded the National Institute of Health – UT El Paso BUILDing Scholars Undergraduate Student Mentoring Award of Excellence.

Steroid estrogen analogues as potential drugs with targeted action

Dr. Svetlana N. Morozkina*, Prof. Alexander G. Shavva, Dr. Alan F. Fidarov, Prof. Vladimir V. Vinogradov
ITMO University, Russia

Steroid estrogens being sex female hormones play crucial role in the functioning of male and female organisms. After menopause, the estrogen level is tragically decreased that causes many disorders like osteoporosis, dementia and cancer development. In this presentation, we will discuss about new modified analogues of steroid estrogens which have been developed in our group as osteoprotectors, cardioprotectors and anti-cancer agents. We present the data covering many aspects of drug design: molecular docking, total synthesis details, pre-clinical investigations, structure-biological activity relationship. New data in the field of most perspective area - the inhibitors of estronesulfatase as new anti-cancer agents - also will be discussed. The developed potential drugs have the improved biological profile in comparison with clinically used medications. At the same time, they have targeted activity which equal or higher compared to known clinically used compounds.

We found analogues with high osteoprotective action and decreased hormonal activity, which are perspective molecules for hormone replacement therapy. The analogues with high cardioprotective activity and without hormonal activity are the best candidates for the prevention and treatment of cardio-vascular diseases. The developed estrogen analogues with high (comparable to endogenous estradiol) antioxidant activity may be very useful for the treatment of neurodegenerative diseases like Alzheimer. On the basis of experimental data we developed the model for the prediction of antioxidant activity. We also demonstrated the possibility of the creation of hybrid molecules with synergic action. These compounds highly active against prostate and breast cancers. For the first time, we illustrated that modified estrogens may be active against triple-negative breast cancer cells.

Takeaway Notes:

- New data about modified estrogen analogues as potential medications with targeted action.
- The knowledge about drug design approaches in the field of modified estrogen analogues.
- Molecular docking as effective tool for the introduction of modifications in steroid skeleton for the selectivity of action.
- The presented data will be useful for scientists working in drug design and application, mainly in the field of anti-cancer agents and hormone-replacement therapy.
- Most of all data in the presentation are new and not published yet. The data may be used as basis for lecture courses and practice illustration of the development of medications with targeted activities. New ideas about the different applications of the developed drugs in other areas may arise. The potential drugs may be useful for the creation of new hybrid molecules with enhance activity.
- The presented results may be used for researchers for clinical application, pre-clinical investigations as well as for the consideration of the creation of new formulations and conjugates which may be new platform for the drugs with high effective targeted action. The data may be used also for students and PhD students as illustration of drug design and application.
- The pre-clinical data obtained illustrate the high effectiveness of new analogues as compared with approved medications and the efficacy and safety are much better as it is known.
- The therapeutic significance of estrogens is quite broad, and thus the obtained new perspective molecules may be investigated in various assays and models in other research groups to extend and to share the knowledge about new properties of estrogen analogues.

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Biography

Dr. Svetlana Morozkina was graduated from Saint-Petersburg State University (Russia) in 1997 – Department of organic chemistry, Chemistry Faculty. She defended her PhD degree at the same Department and, then she got the Post-Doc position from the Government of Russia for young talent people (Saint-Petersburg State University, 1997-2001). In 2004 she organized the research group under the guidance of Professor Alexander Shavva (he was the head of the Department of Natural Compounds Chemistry for 25 years: 1988-2014) and started her research in the field of the total synthesis, investigation of structure and biological properties of synthetic steroid estrogen analogues. She is author of 48 articles, Russian patents and international patents (total 15 patents). In 2017 she moved her group to ITMO University.

The bone-cartilage interface: A complex biological barrier with potential therapeutical targets

¹Előd Ernő Nagy, M.D., Ph.D., ²Béla Kovács, Ph.D.student, ³Emőke Horváth, M.D., Ph.D

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³Emőke Horváth, M.D., Ph.D., Assoc.Prof., Dept. of Pathology, University of Medicine and Pharmacy Târgu-Mureș, Romania

The crosstalk of cartilage and subchondral bone is thought to be a central process in the regulatory pathways of osteoarthritis (OA). Histological changes in OA comprise degeneration and decellularization of the cartilage, elevated bone turnover and subchondral bone attrition. Our research Group, along others recently described that subjacent bone marrow changes are also detectable in animal models with advanced disease stages.

An increasing number of findings attest that the junction of the cartilage and bone is a complex interface, with versatile metabolic interactions and blood vessels penetrating to the close proximity of deep cartilage.

Osteoblasts, osteoclasts and chondrocytes are the key cellular elements of osteoarthritis progression. Their crosstalk seems to be rather subchondral bone-driven, and is influenced by at least 3-4 major signaling pathways. Among these, the OPG/RANKL/RANK system regulates the differentiation of osteoclasts. In human osteoarthritic cartilage, an increased RANKL/OPG ratio was highlighted. We found high levels of osteoprotegerin (OPG) in the synovial fluid of OA patients in comparison with their serum levels, however, no significant difference between synovial OPG of early and advanced OA could be demonstrated. The Wnt/ β -catenin signaling pathway contains other important regulatory molecules which may be crucial for the development of OA. Wnt agonists, like WISP-1, Wnt 16 and Wnt 2-B are active in the osteoarthritic cartilage and provoke important matrix degradation. Increased levels of inhibitors, like serum Dickkopf-1 (DKK-1) or sclerostin were associated with slow disease progression, while DKK-1 antisense oligonucleotids protected the cartilage and reduced bone turnover in animal models. Moreover, the Wnt/ β -catenin signaling pathway interacts with some of the cytokine signaling pathways (TGF β). The growing evidence of pronounced effects confer a special importance to actors of the Wnt-signaling pathway, some of these being proposed molecular targets of specific biological therapy. We present primary research results referring to Wnt gene expression and protein synthesis in different phases of osteoblast differentiation, in order to focus attention on the possibilities of Wnt-pathway modulation.

Takeaway Notes:

- The cartilage-subchondral bone interface is an important barrier with regulatory roles in osteoarticular diseases.
- The cellular elements of the interface with intensive crosstalk are osteoblasts, osteoclasts and chondrocytes.
- The OPG/RANKL/RANK and the Wnt/ β -catenin pathways are key regulatory mechanisms in osteoarthritis progression.
- Some antagonists of the Wnt signaling pathway are candidate molecular targets for specific therapy in osteoarthritis.
- Further understanding of the Wnt pathway's role in osteoarthritis could define novel mechanisms of pharmacological interest.

Biography

Előd Ernő Nagy is Associate Professor at the Department of Biochemistry and Environmental Chemistry, Faculty of Pharmacy, and also Vice-rector of the University of Medicine and Pharmacy, Târgu-Mureș, Romania. He has 18 years experience in basic and clinical research, with a primary focus on diagnostic and prognostic biomarker definition, in chronic joint, bone and cardiovascular diseases. He has a special interest for the multicellular regulation of cartilage homeostasis and for the role of some important regulatory pathways of cartilage and bone turnover. He is also a senior specialist at the Laboratory of Medical Analyses, Mures Clinical County Hospital. He obtained his medical degree at the University of Medicine and Pharmacy, Targu-Mures.

Improvements of computational optimization of drug-target interactions

^{1,*}Csaba Hetényi, PhD, ¹Mónika Bálint, ²Norbert Jeszenői, PharmD, ³István Horváth

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Optimization of drug-target interactions is a central issue of structure-based drug design. There are fast docking methods available for calculation of the structure and energy of target-ligand complexes. Docking is the computational alternative of experimental structure determination methods such as X-ray crystallography, and it can help to reduce the costs of the drug discovery process. However, there are various limitations of computational docking such as inadequate input geometries of the target or the ligand, lack of convergence criteria during random search, inappropriate water models and force fields. The present lecture focuses on the problematics of water models. We show, how the correct prediction of hydration structure of target-ligand interfaces can help overcoming the above-mentioned various limitations of docking, and improve calculation of drug-target interactions.

Takeaway Notes:

The lecture provides practical examples on improvements of calculation of drug-target interactions with the help of open source program packages such as AutoDock, GROMACS, and MobyWat. Such information will help the members of the audience in future drug design projects and improve the efficiency of their job. The message of the lecture will also help teaching of up-to-date solutions of drug design problems.

Biography

Dr. Csaba Hetényi is an Associate Professor in Pharmacology. He has co-authored research articles in prestigious journals J Am ChemSoc, PNAS, EMBO Reports, Bioinformatics, and is also a co-inventor of US patents. Dr. Hetényi has received more than 1500 independent citations for his research results, has a Hirsch-index of 18 and his works were favorably evaluated by several review articles and research papers. In 2011, Dr. Hetényi won a Talentum Academy Award for his research achievements. His present research interest is focused on the development of pharmacoinformatics tools and molecular pathomechanisms of diseases. Dr. Hetényi collaborates with researchers in Sweden, Estonia, Spain, and the USA.

Towards improved activity and stability of gene therapeutics

Ms Maria Taskova and Dr. Kira Astakhova,* PhD
University of Southern Denmark, Denmark

The main topic that I will discuss is the synthesis of novel peptide-oligonucleotide conjugates (POCs) and evaluation of their therapeutic potential. Our recent data shows that internally labelled POCs (shown in Chart 1) is a promising class of molecules for specific targeting of DNA and RNA in vitro and in vivo.

There is currently an unmet need for reliable, sequence-specific gene therapeutics that can be efficiently delivered into a target cell. For example, specific gene knock down of a mutated oncogene could become a side effect free treatment of cancer, given that the therapeutic is specifically delivered into tumor cells.

Using synthetic DNA and RNA in the therapy of human diseases is an exciting modern paradigm that is getting a growing attention in the research community. Indeed, synthetic oligonucleotides and their assemblies have much to offer to modern biomedicine. In our recent work we developed new peptide-oligonucleotide conjugates that showed advantageous target recognition properties and stability in human serum for over a week (Taskova et al. *Bioconjugate Chem.* 2016). As to the delivery issue, it is known that decorating oligonucleotides with peptides such as CPP and NLS, as well as incorporation of fatty acids aid efficient uptake. This implies that in spite of sometimes being challenging, bioconjugation of oligonucleotide opens up exciting opportunities for the new class of therapeutics with previously unachievable activity in vivo.

Our new approach provides an effective practical solution to a problem of developing stable and effective gene therapeutics. Simultaneously, our findings could simplify the development of new gene therapeutics. Other benefits of our research on peptide-oligonucleotide conjugates are chemical advances of the oligonucleotide chemistry and bioconjugation.



Chart 1. Internally labelled POC

Biography

Kira Astakhova obtained a PhD degree in bioorganic chemistry in 2009. She continued as a postdoc in the group of Prof. Jesper Wengel at the University of Southern Denmark. In 2012 she became an Associate Professor at the University of Southern Denmark. Until 2015, she was also a visiting professor at the University of California Santa Barbara, Department of Chemistry and Biochemistry, and at Stanford University, USA. She is the author of 35 research publications, 4 book chapters and 2 patents. She was awarded with several research prizes and fellowships including Marie Curie Early Stage Research Training Fellowship and Lundbeck Foundation research prize. Her research interests are interdisciplinary, combining organic chemistry, biomedicine, biophysics and nanobioscience.

Smart lipid nanocarriers: Potential for intracellular targeting

Vandana B. Patravale, Ph.D
Institute of Chemical Technology, India

Intracellular delivery of anticancer drugs and therapeutic genes (DNA, siRNA, shRNA etc.) is a challenging task faced by pharmaceutical formulators necessitating the need for effective strategies which facilitate superior transfection and endosomal escaping ability. Taking this into consideration, we have designed and synthesized a novel amphiphilic, cationic heterolipid. This cationic heterolipid was employed in fabrication of smart nanocarriers namely cationic self-microemulsifying drug delivery system (C-SMEDDS) for etoposide and monoguinoplex for gene therapy. C-SMEDDS (size <50 nm and zeta potential +32.6 mV) exhibited significant in vitro antiproliferative activity against B16F10 cell line. C-SMEDDS were observed to localize in cytoplasmic, perinuclear and nuclear space of cancer cells and mechanistic studies revealed clathrin mediated pathway, cytoskeletal reorganization and energy dependent uptake as the possible cellular entry mechanisms. The in vivo antitumor activity studies in preclinical melanoma tumor model presented superior tumor suppression ability at therapeutic and sub-therapeutic dose with 100% survival without any signs of hepatotoxicity and nephrotoxicity assuring high efficacy and safety. Monoguinoplex comprised heterolipid complex with p53 gene & GFP based plasmid. The complexation resulted in condensation of DNA bulk structure that offered protection to DNA from endonuclease enzymes and the same was confirmed using DNAase protection assay. The mammalian cells transfection assay proved superior transfection with monoguinoplex and was corroborated using confocal and flow cytometry assessment. Overall, the studies revealed not only a significant enhancement in intracellular uptake but also addressed biopharmaceutical issues related to non-site specific drug delivery and associated toxicity. Thus, the developed heterolipid based nanocarriers present a smart platform for intracellular release of cargo.

Takeaway Notes:

- A thought process towards innovative formulation strategy development
 - Researchers will get an outline of in-depth study planning and execution from ideation to product realization
- Key features:
- Next generation novel and efficacious approaches to treat cancer
 - Industrially feasible and scalable platform technology with multitude applications

Biography

Vandana Patravale is Professor of Pharmaceutics at Department of Pharmaceutical Sciences and Technology of Institute of Chemical Technology, India. She has over 100 refereed publications, 8 granted patents, 24 patents in pipeline, 2 trademark registries with over 250 research presentations and 50 invited lectures at major national and international scientific meetings. She has published two books entitled, 'Nanotechnology in drug delivery-A Perspective on transition from laboratory to market' and 'Pharmaceutical product development: insights into pharmaceutical processes, management and regulatory affairs'. She is recipient of prestigious Bill and Melinda Gates Foundation grant to develop the first ever eco-friendly nanovaccine for nasal immunization and was bestowed with esteemed awards like OPPI women scientist award 2015, Best Pharmaceutical Scientist award 2014, VASVIK award 2013, Veneto nanotech award 2013, APTI best teacher award 2012.

Potential of cytotoxic action of the new cisplatin derivative by UV irradiation

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Platinum complexes such as cisplatin [cis-diamminedichloridoplatinum(II)] and its analogues are widely used as very effective chemotherapeutic agents. The anticancer activity of these drugs is related to the hydrolytic release of the labile leaving ligands with concomitant generation of active mono-aqua and/or diaqua-platinum(II) species that are able to bound nuclear DNA and effectively inhibit transcription machinery. However, the use of these drugs in clinical practice is limited by a number of side effects and their effectiveness in cancer therapy is limited by the acquired resistance. These limitations are impetus for the development of new platinum compounds with lower toxicity which can be activated by light selectively in the target cancer cells. Among platinum photoactivatable compounds, platinum(IV) prodrugs containing azide ligands have attracted great attention. Besides Pt(IV), biological properties of platinum(II) compounds have been also shown to be affected by irradiation with either UV or visible light. The cytotoxic effect of antitumor ineffective transplatin can be also enhanced by UVA irradiation. In contrast to transplatin, the biological action of cisplatin is not affected by irradiation with UVA or visible light. In this study the cytotoxic activity of the new cisplatin analogue bearing a nonleaving 1-methyl-7-azaindole ligand cis-[PtCl₂(NH₃)(1M7AI)] (1M7AI = 1-methyl-7-azaindole, complex 1) was investigated. The mechanism of its cytotoxicity on molecular or cellular level was tested as well. Compound 1 was cytotoxic in all cell lines tested including cisplatin resistant A2780 cells and also in MCF-7 cells (inherently resistant to cisplatin). This complex 1 showed selectivity for tumor cells relative to the nontumorigenic, normal cells comparable with cisplatin. The results also indicate that the cytotoxicity of cis-[PtCl₂(NH₃)(1M7AI)] can be substantially potentiated by UV A and that the mechanism underlying this effect involves Pt-DNA adducts rearrangement as well as ROS generation and DNA cleavage.

Takeaway Notes:

The findings of the present work help to explain the different cytotoxic effects of photoactivated 1 and conventional cisplatin and thereby provide new insights into mechanisms associated with the antitumor effects of platinum complexes photoactivated by UVA and visible light.

Biography

Jitka Prachařová studied molecular and cell biology at the Department of Cell Biology and Genetics, Palacký University in Olomouc before moving to the Department of biophysics in 2010 to work on her dissertation under the supervision of prof. Kašpárková. The topic of her dissertation was Role of DNA modifications by metal complexes in cancer therapy. Following the completion of her PhD in 2013 she accepted an offer to work as a postdoc in the Laboratory of molecular biophysics and pharmacology of prof. Viktor Brabec in the Department of biophysics at the Palacký University in Olomouc. During her work, she completed research fellowships at Institut of Pharmacy, Ernst-Moritz-Arndt University Greifswald, Germany and Photobiology Unit, Ninewells Hospital & Medical School, Dundee, Scotland. The emphasis of her present research is to study the mechanism of new metallodrugs' anticancer activity.

Impact of gut microbiota-mediated bile acid metabolism on the solubilization capacity of bile salt micelles and drug biopharmaceutical properties

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The symbiotic cohabitation of man and microbe has gained increasing recognition as a determinant of the health status of the human host, affording new insights into disease pathogenesis, as well as novel therapeutic targets. From an oral drug delivery perspective, pharmacokinetic research at the host-microbe interface has, to date, been largely concentrated on effects on drug metabolism. The objective of this oral presentation is to provide overview possible mechanisms by which the activity of the gut microbiota might influence the drug absorption process, for example by modulating passive uptake. In the gastrointestinal lumen, bile salts produced by the host are biotransformed by the gut bacteria. This gut microbiota-mediated bile acid metabolism may, by virtue of altering the bile acid pool, affect intraluminal drug solubility and consequently drug absorption.

To discuss the possible impact of bile acid metabolism on intraluminal drug solubility, in vitro data comparing the solubilization capacity of host- versus microbe- derived bile salt micelles for 9 drugs will be presented. Briefly, this data indicates that deconjugation of the bile acid steroidal core (mediated by microbial bile salt hydrolase in vivo) could marginally affect micellar solubilization capacity for some poorly water-soluble drugs (PWSDs). Contrastingly, dehydroxylation of the bile acid nucleus (microbial 7α -dehydroxylase activity) resulted in a statistically significant difference ($p < 0.05$) in bile micelle solubilization capacity; an effect which was observed for all of the model PWSDs tested (Figure 1.). The different magnitudes of solubility enhancement observed for these PWSDs will be discussed with respect to 3 physicochemical descriptors, namely Log P, melting point and polar surface area. In order to progress the physiological relevance of these findings, solubility, dissolution and preliminary permeability data in biorelevant media containing host- versus microbe- derived bile acids will additionally be presented and discussed.

In conclusion, potential mechanisms (identified in vitro) by which the gut microbiota might affect the drug absorption process and thereby drug activity will be presented. Should these findings translate in vivo, disruption of the gut microbial ecosystem could contribute to altered drug solubilization and absorption amongst patient cohorts.

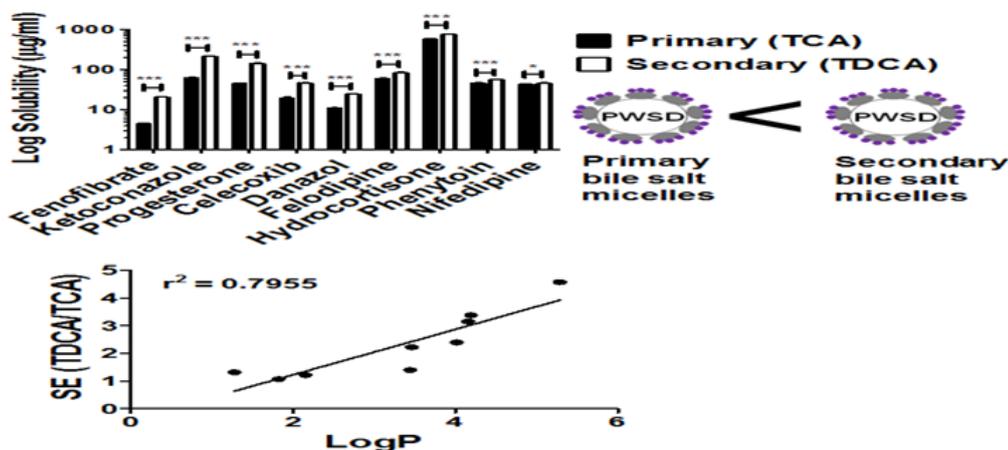


Figure 1. Solubilization capacity of primary (host- derived taurocholic acid (TCA)) versus secondary (microbe-derived taurodeoxycholic acid (TDCA)) bile salt micelles for a selection of PWSDs ($n = 3$, mean \pm SD). The magnitude of solubility enhancement in dehydroxylated microbe-derived (TDCA) bile salt micelles was found to be strongly correlated with PWSD lipophilicity (LogP).

Learning objectives

- To differentiate between host- and microbe- derived bile acids and to gain an appreciation of their altered physicochemical properties.
- To identify the key physicochemical descriptors influencing the differential solubilization of PWSDs by host- and microbe- derived bile salt micelles.
- To discuss the potential significance of altered bile acid “signatures” in the context of biopharmaceutical oral dosage form assessment.

Takeaway Notes:

- The aim of the outlined oral presentation is to provide an insight into the possible mechanisms by which the gut microbiota may affect PWSD solubility, dissolution and permeability. It is envisaged that this topical subject matter will stimulate discussions regarding the need to consider the processes of the gut microbiota, as well as the target subject, the human host.
- The audience is also expected to benefit from discussion regarding a design-of-experiment approach to establishing an in vitro model to assess the impact of different bile salts on drug permeability/activity, which could be used to address other scientific questions.

Biography

Elaine Enright is a registered pharmacist, having graduated from University College Cork, Ireland, in 2014 as “Highest Achieving Student” in the BPharm degree. Elaine subsequently obtained a Masters in Pharmacy from the Royal College of Surgeons in Ireland in 2015. During her studies, Elaine gained experience in the pharmaceutical and regulatory sectors at Servier Laboratories Ireland and at the Health Products Regulatory Authority. Elaine is presently pursuing a PhD in Pharmaceutics, funded by an Irish Research Council Government of Ireland Postgraduate Scholarship. Elaine’s PhD research, which is a collaboration between the APC Microbiome Institute and the School of Pharmacy, UCC, is supervised by Dr Brendan Griffin, Dr Cormac Gahan and Dr Susan Joyce. This four year trans-disciplinary work programme seeks to explore the effect of the gut microbiota on altering drug uptake from the gastrointestinal tract and, in particular, the potential clinical implications of this interplay. It is expected that this research will uncover new mechanisms by which the microbiota can influence individual patient responses to medicines.

Development of intravenous form of rifapentine and its in vivo evaluation

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Rifapentine is a semisynthetic rifamycin antibiotic highly active against a broad spectrum of microorganisms including *Mycobacterium tuberculosis*. Rifapentine solubility in water is very low (0.1 mg/ml); therefore, its dosage forms are currently limited to tablets or capsules (e.g. Priftin®). At the same time, development of water-compatible injectable formulations would extend its clinical potential. Therefore, the objective of the present study was to investigate the applicability of proteins: human serum albumin, succinylated gelatin, and sodium caseinate – for solubilization of rifapentine and evaluate the efficacy and safety of the novel injectable formulations.

The formulations were obtained by precipitation or homogenization yielding freeze-dryable suspensions. Upon reconstitution and proper dilution the lyophilizates formed stable colloidal solutions with the particle size of 10-15 nm suitable for i.v. administration. The best results were obtained with albumin (RFP-HSA) and casein that enabled total concentrations of rifapentine in the aqueous phase of up to 10 mg/ml, which was ~100-fold higher than the solubility of the pure substance.

The antituberculosis effect of RFP-HSA evaluated in Balb/C mice infected with *M. tuberculosis* (H37Rv, ~10⁶ CFU per animal) was similar to that of the oral substance in the lower treatment doses (5 and 10 mg/kg) and appeared to be superior in the highest dose (20 mg/kg).

Based on the moderate LD50 value (340 mg/kg) in BDF mice, the RFP-HSA formulation could be classified as low toxic. In the chronic toxicity study (outbred rats) RFP-HSA administered i.v. and RFP substance given per os exhibited similar adverse effects. However, in contrast to conventional oral formulations, the intravenous formulation of rifapentine did not induce any signs of gastrointestinal toxicity and cardiotoxicity, thus suggesting its usefulness for clinical application.

In conclusion, solubilization with proteins appeared to be a promising approach for development of the effective and safe injectable formulations of rifapentine.

Takeaway Notes:

- The possibility to obtain a new form of antibiotic which proved to be safe and effective, is a reason for further research in this field and manufacture of a novel pharmaceutical.
- Water-compatible form of rifapentine is an example how to make poorly soluble substances more soluble and stable in the aqueous media, without use of toxic and synthetic excipients. This technology is practically universal and can find broad application in other fields.

Biography

Konstantin Ostrovskiy is the Research Associate of the Laboratory of Drug Delivery Systems, at Drugs Technology LLC (Russia, Moscow Region, Khimki), a company producing pharmaceuticals and providing research of novel formulations. His 5 years of work in this field have been dedicated to the problems of drug delivery systems, for substances with poor water solubility and bioavailability especially. In his current role, he is an employee at the above mentioned laboratory, developing drug delivery systems, like protein complexes and polymer nanoparticles. His research interests are drug delivery systems and analytical procedures for their characterization. Prior to joining Drugs Technology LLC, he was a Junior Research Associate at Nanosystem Ltd. (Russia, Moscow), also carrying out research in the field of drug delivery systems. He completed his graduate studies at D.I. Mendeleev Russian University of Chemical Technology in Moscow, as an engineer (department of organic chemical technology, chair of pharmaceutical and cosmetic products). At present he is also working at his PhD dissertation at G.F. Gause Institute of New Antibiotics in Moscow.

Green technology approach for development of BCS class II molecule nanoformulation

Vandana Patravale, PhD, Sandip Gite*
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Fenofibrate (FNB), a BCS class II molecule is primarily used in hypercholesterolemia and hypertriglyceridemia. FNB presents a poor bioavailability of 36% due to its low solubility. To overcome the issue of solubility related poor efficacy; a nanosuspension based drug delivery system is proposed which results in a reduction of particle size; thereby facilitating enhancement in solubility and ultimately the bioavailability. The aim of the present study was the development of nanosuspension of fenofibrate using nano by design (NbD) approach. Stirred media milling and microfluidization techniques were compared for its efficiency to produce nanosuspension. The patient-centric quality target product profile (QTPP) and critical quality attributes (CQAs) were earmarked. Critical formulation parameters (CFPs) such as drug:stabilizer ratio and critical process parameter (CPPs) were identified as high impact parameters affecting particle size and polydispersity index (PDI) in risk assessment studies. The nanosuspension was further evaluated for dynamic light scattering (DLS), zeta potential, in-vitro release, in-vivo pharmacokinetic studies, intrinsic solubility, DSC, SEM, TEM, XRD, FTIR studies.

Takeaway Notes:

- The current research deals with the nanonization of the BCS class-II molecule using green technology approach which is the great learning for the audience.
- The present research deals with the semicontinuous/continuous process of nanoparticle generation using existing technologies, which would help to other researchers to explore the same technology for the other challenging molecules.
- The formulation development was carried out using quality by design (QbD) Approach which enables the efficient and accurate development of the formulation. QbD is the systemic approach to develop any formulation which will help the researchers in their own research areas.

Biography

Sandip M. Gite, is the PhD research scholar in the Institute of Chemical Technology, Mumbai. He has done Masters in Technology from the University Department of Chemical Technology, Dr. BAM University, Maharashtra, India. His research area includes process development for the continuous generation of nanoparticles and translating the batch processes to scale up level. Moreover, he has worked on the modified release drug delivery system. He has 8 national and international publications to his credit. He also co-authored one book chapter in the book entitled, "Pharmaceutical Product Development" from CRC press.

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