ORBIS Final Conference
5-6th July 2023, Poznań

BOOK of ABSTRACTS

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Welcome message

On behalf of Poznan University of Medical Sciences (PUMS) - the ORBIS Project Coordinator and the Scientific and Organizing Committees of the Final ORBIS Conference on July 5th – 6th, 2023 in Poznan, we are honored to warmly welcome the lecturers, participants and guests from Czech Republic, Finland, Germany, Ireland, Slovenia, Serbia, Ukraine, United Kingdom, United States and Poland.

ORBIS (Open Research Biopharmaceutical Internships Support) is an international and intersectoral project funded by the Horizon 2020 - Marie Skłodowska Curie Actions - Research and Innovation Staff Exchange programme implemented between the 1st of March 2018 and the 31st of August 2023. According to the RISE scheme, during the implementation of the goals of the ORBIS project, we have promoted international and inter-sector collaboration through research and innovation staff exchanges and sharing of knowledge and ideas from research to market and vice-versa.

Currently, the ORBIS Consortium consists of thirteen organizations: six European universities – *Trinity College Dublin*, TCD (Ireland); *University of Helsinki*, UH (Finland), *University of Chemistry and Technology Prague*, UCTP (Czech Republic), *University of Ljubljana*, UL (Slovenia), *Poznan University of Technology*, PUT (Poland), *Poznan University of Medical Sciences,* PUMS (Poland), two universities from US – *Rutgers, The State University of New Jersey*, RUTG and *University of Central Florida*, UCF and five pharmaceutical companies: *Applied Process Company Limited*, APC (Ireland), *Physiolution GmbH*, PHY (Germany), *Farmak JSC*, FMK (Ukraine), *Zentiva k.s.*, ZNT (Czech Republic) and *Celon Pharma*, CLN (Poland). All thirteen organisations are involved in activities across the seven work packages of the ORBIS program.

As stated on the ORBIS project website (www.orbisproject.eu), the main research areas of ORBIS cover the synthesis optimization for new active ingredients, preformulation studies, development of novel drug carriers, oral, dermal and transdermal dosage forms, as well as their biopharmaceutical evaluation with the use of novel techniques.

We are finally meeting today after a long break and a few postponements of this Final Conference, initially planned in ORBIS Grant Agreement for December 2021. Our conference brings together esteemed experts, professors, industry representatives, postdoctoral, and early stage researchers including students from several countries in the field of biopharmaceutical research and development. The conference provides them with the opportunity to report, present, share, and discuss scientific questions, achievements, issues and challenges in the field of all main research areas of the ORBIS project mentioned above.

Full of optimism, we are happy that neither the COVID-19 pandemic nor the ongoing war in Ukraine discouraged ORBIS Partners from continuing the project goals. At the same time, we firmly believe that the brave Ukrainian people will soon win this cruel war, and we thank so much our Colleagues from FARMAK they decided to continue participating in our project despite such a difficult time for the Ukraine people.

We would like to thank all the distinguished lecturers who accepted our invitation and all who contributed to organising this event, as well as all participants and guests for coming to Poznan. We wish you all successful, inspiring conference with many novel scientific collaborations and friendships.

Poznań, July 5th, 2023

Prof. Janina Lulek, PhD
ORBIS Project Coordinator

Day 1 - July 5th

Session I - Drug substances and pharmaceutical preformulation

Lecture 1: Andrzej Kutner - Recent advances in API development - prodrug strategies for enhancing the bioavailability of antiviral nucleosides

Abstract

Bioavailability is a prerequisite for effective drug action. *In vivo* bioavailability (intestinal permeability), linked to drug substance solubility and drug product dissolution became the basis of Gordon L. Amidon's Biopharmaceutical Classification System. This classification was adopted by the FDA to waive oral immediate-release drugs from *in vivo* bioavailability studies. One method of improving the bioavailability of an API is to chemically modify its structure leading to increased lipophilicity and ability to penetrate the lipid bilayer in the cell membrane. These modifications, as pro-drug strategies, involve derivatizing the API by introducing substituents that reduce the hydrophilicity of the molecule. They will be presented in the lecture using the reported examples of Christopher McGuigan's pro-drug strategy, applied this year to obtain antiviral nucleosides not only with enhanced bioavailability but also activity. These strategies primarily involve the formation and optimization of the structure of phosphoramidates, esters and amino acid esters, octadecyl phosphates, and *bis*-pivaloxymethyl phosphates. The recently reported optimization of the phosphoramidate prodrug moiety of anti-SARS-CoV-2 nucleoside will be discussed.

Prof. Andrzej Kutner

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Andrzej Kutner received his PhD in organic chemistry from the Chemistry Department of the University of Warsaw (UoW), Poland, his DSc (habilitation) in pharmaceutical sciences from the Faculty of Pharmacy of the Medical University of Warsaw (MUW), and he is full professor of pharmaceutical sciences. He is a trainee at US academia (The University of Wisconsin-Madison, New York University, University of Minnesota, Duluth, University of California, Riverside). He was a Research Director of the Pharmaceutical Research Institute in Warsaw for three terms. At that time, he was one of the initiators of the HORIZON 2020-MSCA-RISE "ORBIS" project. Now, he works at the Department of Drug Chemistry, Faculty of Pharmacy of MUW. He is lecturing on instrumental analysis in drug development at the Faculty of Pharmacy of MUW and strategies of pharmaceutical syntheses at the Chemistry Department of UoW. His main area of interest is medicinal chemistry, the design and synthesis of biologically active substances, and the correlation between biological activity and molecular structure. At present, he is a Co-chair of the HORIZON-MSCA-DN-2023-2027 international project on the eradication of cancer stem cells using synthetic agonists and antagonists of nuclear receptors.

Lecture 2: Stane Srčič - Effect of moisture on solid-state stability

Abstract

Water is an ageless enigma, serving as a major constituent of the Earth's hydrosphere. It is the only chemical substance known to naturally exist in three distinct physical states. Within pharmaceutical systems, water assumes different physical phases and plays a critical role in the development, manufacturing and storage of pharmaceuticals. It influences a wide range of physicochemical and microbiological properties of the active drug substance, excipients, and the final drug product. The interaction of water with solid components can bring about significant physical changes, affecting molecular properties, bulk properties, and the overall performance of the final product. These interactions may also lead to undesirable changes in chemical stability, such as protein denaturation or degradation of active ingredients. Consequently, the adverse impact of water on physical and chemical stability can shorten the shelf life of the products, which is commercially undesirable. In addition to its effects on active ingredients, water can also impact excipient functionality, impairing its intended role in the formulation or potentially triggering other adverse interactions within a multi-component formulation, thus compromising its quality. Water is intricately linked to the microbiological quality of ingredients and drug products, representing an inherent aspect of their overall quality and acceptance. Therefore, a deep fundamental understanding of these underlying interactions is imperative for manufacturing robust drug products with the required quality attributes.

Prof. dr. dr. h.c. Stane Srčič, MSc Pharm (retired)

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Stane Srčič obtained his MSc Pharm and PhD degrees from the University of Ljubljana. After a brief period in the pharmaceutical industry, he joined the Faculty of Pharmacy where he achieved the position of full Professor in Pharmaceutical Technology. Following his PhD, he conducted a Post-Doc at the University of Regensburg, Germany. Initially, his research focused on semisolid systems, later on, he shifted to the study of solids. He actively engaged in research on pellets coating, leading to the development of innovative approaches that have been protected in Europe and the USA. As an educator, he took on responsibilities in the fields of physical pharmacy, pharmaceutical technology, and industrial pharmacy. He actively participated in numerous industrial projects, including various European initiatives. He served as a leader or member of CEEPUS projects for many years. He has (co)authored over 120 scientific articles and has supervised more than 20 PhD students. He is a member of EABs for select European pharmaceutical journals, and he served as a long-standing Member of CVMP at EMA. In 2014, he was honored with the Minarik award, the highest professional accolade in Slovenia and in 2016 he received an honorary doctorate from the University of Szeged, Hungary.

Oral presentation 1: Sreela Ramesh - Non-classical mechanism in crystallization of salts of cyamemazine

Authors: Sreela Ramesh[1,2,] Teemu Tomberg[3], Jan Rohlíček[4], Eliška Skořepová[4], Clare Strachan[3], Miroslav Šoóš[2]

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Cyamemazine is an anti-psychotic drug marketed in its free base form or as its L-tartrate salt. This project explores the non-classical mechanism involved in the crystallization of its L-tartrate salt from suspension. Using in-situ imaging and X-ray diffraction techniques, it is observed that the system passes through an intermediate droplet phase. The imaging of the crystallization is done using non-linear optical method Stimulated Raman Scattering (SRS), polarizing light optical microscopy and fluorescence microscopy. SRS imaging and in-situ X-ray diffraction give information on the chemical make-up of the droplets and the resulting salt form. Since L-tartrate is a kryptoracemic salt, which is a rare occurrence, understanding the crystallization mechanism of this salt can be used to achieve a better understanding of how kryptoracemates form and their properties.

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Oral presentation 2: Martin Balouch - Machine learning algorithms for slurry crystallization control

Authors: Martin Balouch[1]; Akeem Olaleye[2]; Georgia Gunning[2], Melba Simon[2], Sharon Davin[2], František Štěpánek[1]

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One of the crucial steps for crude Active Pharmaceutical Ingredient (API) engineering is crystallization. One of the new Process Analytics Tools (PATs) for automated lab reactors (EasyMax/Optimax from Mettler Toledo) on the market are the EasyViewer 100 and EasyViewer 400 [Mettler Toledo]- microscopy probes for direct observation of particles in the reactor. EasyViewer provides great qualitative data (images) that can be directly observed. It would be beneficial if quantitative data could also be extracted from the images.

Therefore, the aim of this work was to make algorithm for image recognition. The desired quantities were Particle Size Distribution and Aspect Ratio of the particles. The Detectron2 Mask R-CNN FPN convolutional networks were successfully used for the instance segmentation in crystallization experiments. The training was performed using 163 images of benzoic acid crystals and a variety of hyperparameters was tested. The quality of instance segmentation was not improved by any selection of hyperparameters. Therefore, the quality of annotation is determined in this study to be the most crucial parameter for the quality of output. The addition of needle-shaped mannitol crystals and oil droplets allowed the network to be able to distinguish the oiling out during the crystallization.

Funding: Part of the research was funded by the European Union's Horizon 2020 Research and Innovation program under the Marie Skłodowska-Curie grant agreement No 778051. The views expressed in this article are those of the authors and do not necessarily reflect the European Union's or the respective institution's position on the subject.

Session II - Dosage forms and drug delivery systems

Lecture 1: Clare J. Strachan - New insight on solid dosage form analysis

Abstract

Microscopic chemical and solid-state structures and their changes in solid drugs and dosage forms can profoundly affect pharmaceutical performance and patent safety. Despite this, their detailed spatially-resolved analysis can be difficult or impossible with established analytical technologies. Multimodal non-linear optical imaging represents opportunities for sensitive and specific chemical and solid-state pharmaceutical imaging. Non-linear optical imaging encompasses several nonlinear optical phenomena, including coherent anti-Stokes Raman scattering (CARS), stimulated Raman scattering (SRS), sum frequency generation (SFG), and two-photon excited fluorescence (TPEF). Imaging in 3D with (sub)micron resolution is rapid, non-destructive, possible *in situ* in aqueous media, and generally does not require prior sample preparation. This talk will explore several applications of non-linear optical imaging for solid drug and dosage form analysis. The link between characterisation and critical quality pharmaceutical attributes will also be considered.

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Clare Strachan's research primarily advances pharmaceutical analysis with vibrational spectroscopy and imaging. She has a particular interest in Raman, coherent Raman and other forms of non-linear optical methods to better understand and optimize drug and dosage form behaviour (e.g. during manufacturing, storage, administration and drug delivery). She is currently the recipient of a Finnish Research Impact Foundation Tandem Industry-Academia Fellowship, during which she is based at Orion Corporation in Finland and investigates multimodal nonlinear optical imaging to enlighten the solid-state behaviour of drug particle and dosage form surfaces.

Clare Strachan originates from New Zealand where she completed a PhD in 2005 on the spectroscopic characterisation of solid state drugs at the University of Otago. During this time she was also based at TeraView Ltd and the Cavendish Laboratory, University of Cambridge, UK, where she employed terahertz spectroscopy for solid state pharmaceutical analysis. Since then she has oscillated between Finland and New Zealand, and is now Professor of Pharmaceutical Analysis at the University of Helsinki where she heads the Formulation and Industrial Pharmacy Unit within the Faculty of Pharmacy. She has published approximately 125 articles in international scientific journals as well as several book chapters, has supervised about 20 PhD students.

Lecture 2: Dimitrios Lamprou - Emerging technologies transforming therapy

Abstract

The advancement of healthcare therapies is under constant development due to changing demographics and evolving disease-states. To ensure continuous furtherance of the healthcare system capacity to treat such ailments, emerging technologies are coming to the forefront of medicine. It's the hope that these technologies are capable of covering a broad scope of therapeutic treatment areas, enabling novel pharmaceutical pathways to be established. In this talk, a few of these emerging technologies will be discussed, such as, additive manufacturing (e.g., 3D Printing, 4D Printing, Bioprinting), microfluidics and lab-on-a-chip, Bio microelectromechanical systems (BioMEMS) and machine learning (ML), with examples from our state-of-the-art-lab.

prof. Dimitrios Lamprou

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Dimitrios Lamprou (Ph.D., MBA) is Full Professor (Chair) of Biofabrication and Advanced Manufacturing, and Director at MSc Industrial Pharmaceutics at Queen's University Belfast (QUB). He is also the Chair at United Kingdom and Ireland Controlled Release Society (UKICRS) and the Chair of the Academy of Pharmaceutical Sciences (APS) Emerging Technologies Focus Group. Dimitrios, is the author of over 150 peer-reviewed publications, has over 350 conference abstracts, has given over 150 Invited Talks in institutions and conferences across the world, and has secure Funding more than £3.5M. Dimitrios has been recognised as world leader in 3D Printing & Microfluidics. PubMed-based algorithms placed him in the top 0.088% of scholars in the world writing about 3D Printing and on the top 0.071% of scholars in the world writing about microfluidics, in the past 10-years. Moreover, PubMed-based algorithms placed him in the top 0.63% of scholars in the world writing about nanofibers. Dimitrios has also been named in the Stanford University's list 2021 & 2022 of World's Top 2% Scientists, for his research in Pharmaceutics and Biomedical Engineering. His research and academic leadership have been recognized in a range of awards, including the Royal Pharmaceutical Society Science Award and the Scottish Universities Life Sciences Alliance Leaders Scheme Award. For more info, please visit www.emergingtechnologieslab.com/.

Oral presentation 1: Dominik Martynek - Solid solutions preparation using spray drying and hot melt extrusion

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Low solubility is a common problem in the pharmaceutical industry that can result in poor bioavailability of orally administered drugs. This can lead to high doses, higher dosing frequency, and more pronounced side effects. To address this issue, we produced amorphous solid solutions of a drug product stabilized with a polymer. Although this approach results in a less stable product on the shelf, it provides a better dissolution profile. Therefore, the final formulation needs to be optimized to meet strict criteria set by regulatory authorities.

In this work, we either spray dried, or hot melt extruded indomethacin with PVP K30 or HPMC E5 to produce solid solutions. We evaluated physical characteristics of the solid solutions and compared their intrinsic dissolution rates. This allowed us to compare the two production methods, identify their strengths and weaknesses, while also gaining valuable knowledge for continuous manufacturing of pharmaceuticals.

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Oral presentation 2: Anna Froelich - Topical delivery of meloxicam using liposome and microemulsion formulation approaches

Authors: Julia Zhang[1,2], Anna Froelich[3], Bozena Michniak-Kohn[1]

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Topical drug delivery systems with non-steroidal anti-inflammatory drugs (NSAIDs) can provide numerous advantages over oral ones, e.g. the possibility to avoid first pass effect and the reduction of the gastrointestinal side effects. However, the barrier function of the skin impairs the penetration and absorption of drugs. Numerous formulation strategies, including liposomes, nanoparticles, micro- and nanoemulsions etc., have been proposed to overcome the function of stratum corneum and to improve the transport into the skin.

The aim of the study was to develop, characterize and compare conventional liposome, deformable liposome (transfersome) and microemulsion formulations as potential topical delivery systems for meloxicam. Liposomes were tested for vesicle size, zeta potential and entrapment efficiency. For microemulsions, particle size, electrical conductivity and viscosity were checked to assess the structure of the investigated systems. An ex vivo skin permeation study has been conducted to compare these formulations. The dermal and transdermal delivery of meloxicam using these formulations can be a promising alternative to conventional oral delivery of non-steroidal anti-inflammatory drugs (NSAIDs) with enhanced local and systemic onset of action and reduced side effects.

The performed studies allowed for optimization of the preparation method and the composition of the investigated systems. The comparative skin permeation studies performed for the obtained systems revealed that the highest flux and permeation values were obtained for transfersomes, indicating these drug carriers as the most promising in terms of topical drug delivery.

Funding: Part of the research was funded by the European Union's Horizon 2020 research and innovation program under the Marie Skłodowska-Curie grant agreement No 778051 and the Ministry of Science and Higher Education of Poland fund for supporting internationally co-financed projects in 2018–2022 (agreement No 3899/H2020/2018/2). Funding for this study was provided by the Center for Dermal Research (CDR), Rutgers, The State University of New Jersey, Piscataway NJ 08854 USA.

Oral presentation 3: Viktoriia Shyrokova - Comparative studies of gels for topical delivery of ketoprofen: physicochemical characteristics and in vitro drug release rate determination

Authors: Viktoriia Shyrokova[1], Kateryna Kosarieva[1], Yuliya Kondratova[1], Petro Pyzh[1], Inna Cherniuk[1], Anna Froelich[2], Tomasz Osmałek[2], Mirjam Gosenca Matjaž[3]

[1]Farmak JSC, Kyiv, Ukraine [2]Poznan University of Medical Sciences, Poznan, Poland, [3]University of Ljubljana, Faculty of Pharmacy, Slovenia

Pharmaceutical products in the form of gels containing non-steroidal anti-inflammatory agents are the most widely used local analgesics for inflammation of joints, muscles, ligaments and tendons of rheumatic or traumatic origin. In the process of pharmaceutical development of such drugs, it is necessary to take into account factors affecting pharmacological equivalence (rheology, texture, consistency, release of API).

During the internship, comparative studies of the rheology (both flow behavior and viscoelastic properties) of generic formulation containing ketoprofen (Nobi-Gel) and similar original Ketonal formulation were conducted. Carbomer is used as gelling agent in both formulations. Tests were performed on Haake RheoStress 1 rheometer, plate-plate system and Anton Paar FT-A-VMT-02 rheometer, cone-plate system. Comparative studies of texture and consistency were conducted using Autograph AGS-10kNX (Shimadzu) universal analyzer.

Comparative studies of drug release rate determination (IVRT) using different cell apparatus according to USP (1724) were also conducted. IVRT were performed on vertical Franz diffusion cells and flow-through cell using SnakeSkin™ (ThermoScientific; MWCO: 10K) dialysis tubing and Strat-M membranes.

The obtained results of studies of rheology, texture, consistency and IVRT for Nobi-Gel and Ketonal showed a significant effect of different types of carbomer on rheological properties and no effect on the release rate of ketoprofen.

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Session III – Biopharmaceutical evaluation of dosage forms and drug delivery systems

Lecture 1: Iztok Grabnar - Modeling complex absorption in a population pharmacokinetic analysis using empirical functions

Abstract

Drug absorption processes are complex and highly variable, but in a population pharmacokinetic analyses we often lack the data to build mechanistic absorption models. We typically rely on simple absorption models (zero-order, first-order, or mixed-order). Simple absorption models may sufficiently describe the pooled data, but individual pharmacokinetic profiles may indicate delayed absorption or multiple irregular peaks. This talk will focus on various parametric absorption models, including inverse Gaussian, Erlang, and transit compartment model; as well as convolution-based model with a nonparametric input function. Although empirical, these models are flexible and allow estimation of the variability of the absorption processes and investigation of the covariate effects when mechanism-based absorption models become too complicated to estimate the parameters. Application of the modelling and simulation to bioequivalence study design and bioequivalence analysis procedure (model-informed and model-integrated bioequivalence assessment) will also be addressed.

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Iztok Grabnar is Full Professor of Biopharmaceutics and Pharmacokinetics at University of Ljubljana, Faculty of Pharmacy. His research experience is in pharmacometrics, focused on the development of modelling and simulation methods for biomedical systems. He applies these methods to studies in the fields of biopharmaceutics, pharmacokinetics and clinical pharmacology. His main research interest is in nonlinear mixed effects modelling to better understand the variability in pharmacokinetics and pharmacodynamics and optimize pharmacotherapy in individual patients.

Iztok Grabnar obtained his PhD in 2000 on pharmacokinetics of intravesical instillation from University of Ljubljana Slovenia. He was involved in many industrial projects, he was Vice-Dean for international relations at the Faculty of Pharmacy, University of Ljubljana (2015-2019) where he is teaching pharmacokinetics and biostatistics. He has published approximately 100 articles in international scientific journals and has supervised 11 PhD students. He is a recipient of the University of Ljubljana Faculty of Pharmacy award for a significant contribution to the esteem of the University of Ljubljana and to the development of many young professionals (2019).

Lecture 2: Irena Tomaszewska - Applications of biopredictive tools during drug product development

Abstract

Historically, a typical drug development program took on average 10 years from first-in-human trials to market approval. Nowadays, this process is accelerated to 7 years or in some cases much less. That degree of acceleration is only possible with application of biopredictive tools. Using a combination of biorelevant in vitro systems and in silico Physiologically Based Phamacokinetic Modeling (PBBM), in combination with agile and information- rich clinical study design enables the rapid development of drug product. The aim of this presentation is to identify possible biopharmaceutical challenges for this strategy and provide insight into in vitro methodologies and technologies that could help to address those challenges

Dr Irena Tomaszewska
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Dr Irena Tomaszewska has been working at Pfizer R&D in Sandwich, UK for the past 11 years. First 10 years, Dr Tomaszewska was working for Analytical Research Development Department as a dissolution subject matter expert, where she was responsible for the development of QC dissolution methods. Over the past five years, Dr Tomaszewska is leading cross-departmental group that is implementing innovative TIM-1 technology, a unique gastrointestinal model for the prediction of the in-vivo behaviour of oral drug products. Last year, Dr Tomaszewska joined Global Biopharmaceutics group with responsibility for leading the in vitro biopharmaceutics team at Sandwich. She joined Pfizer after completing a PhD in the development of in-vitro and physiologically based pharmacokinetic models for pharmaceutical cocrystals at the University of Bath. Dr Tomaszewska has co-authored 15 publications and two book chapters in support of external collaborations: OrbiTo and PEARRL.

Oral presentation 1: Monika Zielińska - The effects of various food products on bisphosphonates availability

Authors: Monika Zielińska[1], Grzegorz Garbacz[2,3], Jaroslaw Sczodrok[3] and Adam Voelkel[1]

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The bioavailability of orally administered bisphosphonates is very low (<1%) due to their short absorption window in the proximal duodenum and high affinity for food. The food ingredients are able to bind the drug, but the presence of food extends the residence times of bisphosphonates in the absorption window. Therefore, the main goal of this study was to select a group of food products that are characterized by low binding affinity to bisphosphonates and thus will not reduce their availability upon concomitant administration.

The aim of this study was to examine a series of food products in terms of their sorption capacity of bisphosphonates. The sorption capacity, expressed as the mass of the analyte that can be retained on the sorbent, in this case a digested food product, was determined for seven food products. It was proved that the food products with a high content of divalent ions bind high amounts of bisphosphonate.

The obtained results indicate that the oral administration of risedronate should be conducted only with properly selected food components, which do not decrease the free fraction of the drug that can be absorbed.

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Oral presentation 2: Yulia Kondratova - Study of dissolution profiles: from API to IVIVC

Authors: Yulia Kondratova[1], Tetiana Doroshchuk[1], Dorota Danielak[2], Michał Romański[2], Bartek Milanowski[2], Anna Froelich[2], Grzegorz Garbacz[3], Mirjam Gosenca Matjaž[4]

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The study of *in-vitro* dissolution profiles of active pharmaceutical ingredients (API) and drug products is the main laboratory model in the development of the finished dosage forms, such as oral tablets, hard capsules, suspensions, and dermal preparations. This research approach is used at all stages of the development. However, the greatest responsibility is deciding on conducting bioequivalence trial of experimental batches accounting for ethical, safety and commercial aspects.

During the grant internship, different experiments were conducted using various types of equipment, such as: USP I, II, III, IV, vertical Franz diffusion cells and specially designed apparatus for predicting *in-vivo* results. Studies have been carried out on various subjects: API mixtures, semisolid drug products (creams, ointments, gels) and prolonged-release tablets. The final stage was the simulation of the plasma profiles using *in-vitro-in-vivo* correlation (IVIVC) and custom semi-mechanistic IVIV prediction model.

In summary, different approaches were introduced to evaluate similarity of the developed drug product and the reference formulation.

Funding: Part of the research was funded by the European Union's Horizon 2020 Research and Innovation program under the Marie Skłodowska-Curie grant agreement No 778051. The views expressed in this article are those of the authors and do not necessarily reflect the European Union's or the respective institution's position on the subject.

Day 2 - July 6th

Session I - Rutgers University

Lecture 1: Joachim Kohn - Future opportunities in the field of drug delivery research

Abstract

Much of the research priorities in drug delivery research are focused on targeted drug delivery for cancer therapies and a wide range of controlled drug release systems for commonly used active pharmaceutical ingredients (APIs). In this presentation, I will highlight some of the emerging health threats, some of the emerging new APIs, and some of the new scientific discoveries that create new opportunities for drug delivery research. Emerging health threats include viral pandemics beyond COVID, antibiotic-resistant pathogens, the need for new anti-fungal therapies, approaches to address malnutrition, and emerging dis-eases caused by increasing pollution and climate change. I firmly believe that we will see a shift from conventional drugs to biological agents such as peptides, proteins, RNA and DNA, requiring new and different drug delivery systems. As an example, I will highlight my work developing a topical peptide delivery system as a wound dressing for burn patients. This project illustrates the many opportunities to com-bine biotechnology (a new peptide) with polymer science (a new dermal delivery system) to address a medical need for which there is currently no effective treatment.

Prof. Joachim Kohn, Ph.D.

President, International Union of Societies for Biomaterials Science and Engineering
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Joachim Kohn, PhD, FBSE is a national leader in the field of biomaterials science. As founding director of the New Jersey Center for Biomaterials (NJCBM) for 22 years and as Head of the Laboratory for Biomaterials Research at Rutgers, Prof. Kohn has made seminal contributions to the design and commercialization of new biomaterials for regenerative medicine, tissue engineering and drug delivery. He pioneered the use of combinatorial and computational methods for the optimization of polymer properties for use in medical implants (including a coronary stent and an antimicrobial device to prevent infections in pacemaker patients). These implants are being used by over one million patients and are currently approved in 46 countries. As a translational scientist, Prof. Kohn has 78 issued US Patents on novel biomaterials and seven companies have licensed his technologies. He is the scientific founder of three spin-off companies. Dr Kohn retired from Rutgers in 2020 and remains active in research, entrepreneurship and the biomaterials community. He was elected President of the International Union of Societies for Biomaterials Science and Engineering in 2020.

Lecture 2: Prof. Rohit Ramachandran - Energy efficient smart-manufacturing of pharmaceutical solid oral dosage forms

Abstract

The global pharmaceuticals market is a trillion-dollar industry, but the pharmaceutical sector lags in manufacturing innovation and automation which limits its potential to maximize energy efficiency. The implementation of a smart manufacturing (SM) platform can help enterprises create business models, which can be adapted for the energy-demanding manufacturing process to reduce energy consumption while ensuring product quality, thus ensuring more sustainable process operations. In the developed smart manufacturing platform, process data of three unit-operations (granulation, drying and milling) involved in the downstream manufacturing of solid based drugs, are collected using a combination of a manufacturing execution system (MES) and an electronic laboratory notebook (ELN). The collected data are then transferred to a central cloud data lake, from which they can be imported into integrated process models for predicting product quality and energy efficiency. This data is also used to perform techno-economic analysis (TEA) for cost evaluation. The process models are developed using first principle-based techniques which can accurately predict the critical quality attributes of the final product. The energy efficiency of the process is calculated using statistical models relating the power consumption and the process parameters. Using the developed process models and process data from the SM platform, the proposed framework can quantitatively assess the energy and cost savings as the process is being optimized. Utilizing the integrated SM platform, the pharmaceutical manufacturing process is optimized to achieve an energy saving of over 20%.

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Dr. Rohit Ramachandran is currently full Professor at the Dept. of Chemical & Biochemical Engineering at Rutgers University, NJ, USA. His research interests are at the interface of Process Systems Engineering and Particle Technology with applications in Pharmaceutical and Chemical Processes. He has published over 125 journal papers and 8 book chapters in these areas and has presented his work at numerous conferences and invited seminars. His research work has been cited approximately 5000 times with a H-index of 42. He has received several awards such as the National Science Foundation (NSF) CAREER award, the National Institute of Technology and Education (NIPTE) Young Investigator award, the American Institute of Chemical Engineering (AIChE) Quality-by-Design in Drug product manufacturing award, and the Rutgers Chancellor's Scholar and Board of Trustees awards.

Oral presentation 1: Aneta Kalvodova - Innovative cerosomes as carriers for an enhanced dermatitis therapy

Authors: Aneta Kalvodova[1], Bozena B. Michniak-Kohn[2], Jarmila Zbytovska[1]

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Dermatoses are skin diseases caused by lowered level of lipids in the intercellular lipid matrix of skin's uppermost layer *stratum corneum*. A promising therapy for such cases is the application of liposomally formulated skin lipids (ceramides, cholesterol, fatty acids) that replenish the lipids lost due to the skin condition. These so-called cerosomes proved very effective in disrupted skin barrier repair. This unique ability of theirs could be also supported by the addition of an anti-inflammatory drug that takes care of the inflammation often present at the affected sites. The best way of introducing such drug could be by the combination of cerosomes with a great nanovector for topical drug delivery – lipid nanocapsules (LNCs). LNCs showed great potential in both encapsulating and delivering corticosteroids into the respective cutaneous layers. Therefore, the main aim of this work was to create a combined system "cerosomes-LNCs" that would ensure the skin barrier restoration thanks to the ceramides, and simultaneously effectively deliver anti-inflammatory drugs into the deeper layers of the skin tissue. Moreover, thanks to the uncomplicated preparation process of both nanosystems, this formulation has a great potential for the personalization of the product based on the patient's current disease state and prescribed medication.

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Oral presentation 2: Aleksandra Grząbka-Zasadzińska - Prediction of quality attributes of granules prepared by high-shear wet granulation

Authors: Aleksandra Grząbka-Zasadzińska[1], Ashley Dan[2], Koyel Sen[3], Jingzhe Li[3], Paul Shubhajit[3], Tseng Yin-Chao[3], Rohit Ramachandran[2]

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The aim of this study was to explore a reasonable design space for a high-shear granulation process that involves diversity in starting material properties and practical process conditions. Two model API were used: acetoaminophene and ibuprofen sodium dihydrate. Preliminary experiments were run to define appropriate batch size, total amount of liquid added, premixing time, liquid addition time and speed, and RPM.

Experiments were carried out on a batch high shear granulator to generate sufficient data for calibration and validation of the mathematical model. The granules produced were characterized by particle size, and granule porosity/strength. The granules were then milled at two speeds using the Quadro model #197 mill equipped with a square impeller and screen with 1016 µm holes. Cumulative mass output and hold up results were collected. The influence of milling and post-processing parameters on granule properties was studied as well.

A population balance model (PBM) was used to simulate granulation and milling processes used in this study, by tracking the number of particles that change over time due to rate processes such as aggregation, breakage, and consolidation. The performance was determined by the prediction accuracy of granule quality.

Funding: Part of the research was funded by the European Union's Horizon 2020 Research and Innovation program under the Marie Skłodowska-Curie grant agreement No 778051, and the Ministry of Science and Higher Education of Poland 5014/H2020 – MSCARISE/2019/2. The views expressed in this article are those of the authors and do not necessarily reflect the European Union's or the respective institution's position on the subject.

Part of the research was funded by Boehringer Ingelheim Pharmaceuticals Inc

Oral presentation 3: Marta Karaźniewicz-Łada - UPLC-MS/MS method for the stability study and bioanalysis of first-line anti-tubercular drugs

Authors: Marta Karaźniewicz-Łada[1], Katarzyna Kosicka-Noworzyń[1], Prakruti Rao[2], Nisha Modi[3], Yingda L. Xie[3], Scott K. Heysell[2], Leonid Kagan[4,5]

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The rationale for therapeutic drug monitoring (TDM) of anti-tuberculosis (anti-TB) drugs is well documented. The implementation of TDM in routine clinical practice requires an understanding of the limited stability of anti-TB drugs. For this reason, a simple and sensitive UPLC-MS/MS method with a single protein precipitation was developed and validated for simultaneously quantifying isoniazid (INH), pyrazinamide (PZA), rifampicin (RIF), its metabolite 25-desacetylrifampicin and degradation products: rifampicin quinone and 3-formyl-rifampicin. Chromatographic separation was obtained on a Kinetex Polar C18 column (2.6 µm; 150 x 3 mm) with 5mM ammonium acetate and acetonitrile, both containing 0.1% formic acid, in the mobile phase at a flow rate of 0.35 mL/min. The mass detection was achieved using electrospray ionization in the positive ion mode with multiple reaction monitoring. The lower limit of quantification (LLOQ) for RIF and its degradation products was 0.1 µg/mL, 0.05 µg/mL for INH, and 0.2 µg/mL for PZA. The method validation was performed based on the FDA guidance. The detailed stability study of the analyzed compounds was performed at various storage conditions. The method can be further applied to the simultaneous determination of RIF, INH, and PZA, as well as RIF metabolism/degradation products in plasma samples of patients with tuberculosis.

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Session II - University of Central Florida

Lecture 1: Prof. Michał Masternak - Senescent cells as new pharmacological targets for age-related diseases and anti-aging therapy

Abstract

One of major hallmark of aging, cellular senescence has been implicated in the pathogenesis of many major age-related diseases affecting almost all organs in humans' body. This complex cellular process occurs through the lifespan initially playing beneficial roles in a variety of biological processes by promoting embryogenesis, wound healing, and tumor suppression. Yet, time dependent increased accumulation of senescent cells has been connected to many age-related conditions including metabolic disorders, cancer, Alzheimer's disease and related dementias, cardiovascular diseases, and others. Therefore, investigating the detailed mechanism associated with cellular senescence and development of novel methods to reduce or delay the accumulation of senescent cells during aging may attenuate age-related pathologies. Selective clearance of senescent cells in animal models increase lifespan and health span. Our newest studies showed that flavonoids based senolytic therapy in cell culture and in mice promotes selective elimination of senescent cells, reduces inflammation and improves organismal health. These studies indicates that the search for novel senolytic therapies, especially targeting selected specific type of senescent cells represent important future direction towards safe, effective and potentially tissue specific interventions allowing to alleviate age-dependent tissue deterioration and increase disease-free life expectancy.

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Professor Masternak received Ph.D in Biological Sciences from Karol Marcinkowski University of Medical Sciences in Poznan. After completing post-doctoral training in studies of genetics of aging and longevity he started his own research program at Burnett School of Biomedical Sciences at University of Central Florida. In 2019 he was nominated by the President of the Republic of Poland for a Professor of Medical and Health Sciences, and in 2023 he was promoted for a Professor of Medicine at the University of Central Florida. The goal of his laboratory is to study the mechanistic role of senescent cells and senescent-associated miRNAs in process of aging, age-relate diseases and he work on development of pharmacological therapies promoting clearance of senescent cells form the body. During his work on aging and longevity he published 118 original research papers, 18 review articles and 5 book chapters. He is also an active graduate and undergraduate teaching faculty at University of Central Florida, and he serve as an associate editor in several journals including Experimental Gerontology, Journals of Gerontology, GeroSciences, Frontiers of Endocrinology, Reports of Practical Oncology and Radiotherapy and Aging Pathology and Therapies, and he is a standing member of Aging System and Geriatrics study section at National Institute of Health.

Oral presentation 1: Ewelina Juszczyk - The impact of selected miRNAs on growth of head and neck cancer cell lines in vitro

Ewelina Juszczyk[1], Artur Janusz[1], Sarah Ashiqueali[2], Sarah Noureddine[2], Alicja Copik[2], Jeremiah Oyer[2], Igor Piotrowski[3], Pawel Golusinski[4,5], Wojciech Golusinski[6,7], Michał Masternak[2]

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RNA-based drugs to treat cancer are of great interest in the recent years. Potential therapies involve the use of miRNA – a short-chain RNA able to modify the function of genes, including those responsible for carcinogenesis.

The aim of the following study was to determine the impact of a cluster of selected miRNAs, (has-mir-378c, has-mir-6510-p5, has-mir-6510-p3, has-mir-146a) on head&neck cancer cell growth pattern. The expression levels of these miRNAs are significantly reduced in tumors when comparing with healthy tissue from the same patients which is believed to play a role in carcinogenesis. In vitro research was performed using two commercial cell lines: FaDu and Detroit562. This work started with the cell culture and the development of methods to track, visualize and quantify the cell growth, as well as methods to confirm the effectiveness of transfection (RNA extraction and qPCR) of cells with miRNA mimics of interest. The tracking of cell growth was assessed via visualising the cells containing Katushka red fluorescent protein or using the MTS assay.

We concluded that transfection of both cell lines with selected miRNA mimics altered the cell growth pattern, however, the extent of this alteration depended on cell line as well of type of miRNA.

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Oral presentation 2: Błażej Rubiś - New therapies targeting aging cells in the skin

Błażej Rubiś[1], Anna Paszel-Jaworska[1], Aleksandra Dańczak-Pazdrowska[2], Justyna Gornowicz-Porowska[3], Adriana Polańska[4], Violetta Krajka-Kuźniak[5], Maciej Stawny[6], Aleksandra Gostyńska[6], Michał Masternak[7]

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Senescence is accompanied by numerous processes that lead to alterations in cell metabolism, cell cycle arrest, and, eventually, increased production of senescence-associated secretory phenotype (SASP). Consequently, signaling pathways cascades are activated, leading to inflammation that can trigger multiple disorders, including cancer. Recently, a novel therapeutic approach was proposed based on targeting senescent cells using senolytics. This group of biologically active compounds includes fisetin, quercetin, dasatinib, and others. These compounds were shown to affect laboratory animals (rodents) by improving the quality of life and significantly increasing the length of life by reducing senescent cells in different organs. Based on these findings, we decided to evaluate the potential of these compounds in treating human skin using *in vitro* model based on human-derived keratinocytes (HEKa) and fibroblasts (HDFa). Cytotoxicity assay revealed that the activity of the compounds was time- and dose-dependent as well as cell-type dependent. Further studies were performed to reveal the mechanistic aspect of these observations. However, it requires clarification before entering clinical trials to provide not only efficient but, first of all, safe application of senolytics to human skin.

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Poster session- July 5 – 6th 2023

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2. B. Rukowicz, M. Sheehan, S. Davin, **RAMAN SPECTROSCOPY FOR PROCESS ANALYTICAL TECHNOLOGY OF PHARMACEUTICAL MANUFACTURING**
3. P. Gajewski, A. Marcinkowska, L. Ridvan, **DETERMINATION OF THE RESIDANCE TIME DISTRIBUTION OF THE POLYMER-API MIXTURE DURING THE HOT MELT EXTRUSION PROCESS**
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7. A. Zdarta, K. Diakun, I. Nagorichna, **THE IMPORTANCE OF THE QUALITY CONTROL OF THE PREFORMULATION SUBSTRATES**
8. N. Burlaga, J. Hert, E. Bartosińska, O. Dammer, J. Beranek, E. Kaczorek, **COMPATIBILITY STUDIES OF THE API AND EXCIPIENTS (IN THE DRUG FORMULATION) WITH THE USE OF NOVEL TECHNOLOGICAL APPROACHES**

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38. **ORBIS BENEFICIARIES AND PARTNERS**
39. **ORBIS MANAGEMENT - NAVIGATING THE UNFORESEEN CHALLENGES IN A LARGE EU PROGRAM**
40. **ESSENTIAL INGREDIENTS. FROM WP1 TO WP7**
41. 2nd Summer School Best poster award winner: M. Novak, Z. Grof, P. Kovacik, C. Strachan, A. Juppo, F. Štěpánek. **3D PRINTED DOSAGE FORMS, DESIGNED BY THE FDM TECHNOLOGY, MATHEMATICAL SIMULATION AND SYRINGE-BASED PRINTING**
42. 4th Summer School Best poster award winner: M. Balouch, A. Olaleye, G. Gunning, M. Simon, S. Davin, F. Štěpánek. **DESIGN OF PARTICLE SIZE AND MORPHOLOGY**

ORBIS-themed posters (35 – 40) were prepared by:

A. Białek, D. Danielak, S. Davin, K. Filip, A. Froelich, P. Gadziński, E. Jakubowska, K. Kosicka, J. Krysztofiak, J. Lulek, M. Michalak, B. Raducha, P.J. Rudzki.

Work package 1 (WP1)

1. PREPARATION AND EVALUATION OF CO-CRYSTALS OF APREMILAST WITH MONO- AND DICARBOXYLIC ACIDS

Kh. Chemna[1], V. Rudiuk[1], E. Skorepova[2], F. Stepanek[2], J. Rohlicek[3]

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The search for various solid forms of an active pharmaceutical ingredient (API) is an important step in drug development. Almost every solid compound is able to create more than one crystalline arrangement. The fundamental importance of pharmaceutical solid polymorphism is based on the fact that the distinct solid-state forms of the same chemical compound may have different physicochemical properties. The discovered polymorphs, hydrates, solvates, salts, and co-crystals may have different properties, such as thermal stability, solubility, dissolution rate, bioavailability or hygroscopicity, and therefore may have an influence on drug product safety and efficacy.

The goal of our work was to test the co-crystallization ability of API Apremilast with 19 mono- and dicarboxylic acids and to characterize them by powder and single-crystal X-ray diffraction. Neat grinding, liquid assisted grinding and slow evaporation of the solution were used to prepare co-crystals of API with acids.

One of the samples resulted in well-formed and nicely diffracting single crystals. However, further analysis by single-crystal XRD revealed that no co-crystal was formed, and the sample corresponds to the pure and known form of the used co-former, the Stearic Acid. After analyzing all of the obtained powder samples it was found that one of the received forms has a unique PXRD pattern, that didn't have any similarities with the known forms of API and coformer patterns. This promising result, probably a new crystalline solid form of API, was made by grinding API and formic acid without adding any solvent. However, it needs further investigation to describe its crystal structure and confirm our expectations.

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2. RAMAN SPECTROSCOPY - PROCESS ANALYTICAL TECHNOLOGY FOR BIOPHARMACEUTICAL MANUFACTURING

Beata Rukowicz[1], Mark Sheehan[2], Sharon Davin[2]

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Monitoring of critical parameters of chemical and biotechnological processes is an essential tool at every unit stage of drug manufacturing technology. The aim of Process Analytical Technology is, among others, to provide effective tools, such as multidimensional data analysis, modern analytical methods, and monitoring tools for continuous improvement of knowledge. Among the methods of wide interest are spectroscopic techniques that can be used in the control of biotechnological processes. At the design stage of the upstream process, many factors affect the resulting product and process. Optimization involves the verification and selection of cell lines, growth conditions, media, supplementation, type of bioreactor and infection parameters (including MOI - multiplicity of infection, TOI - time of infection).

In process control, inline Raman spectroscopy in combination with multivariate statistical analysis has been identified as a potentially useful tool for advanced bioprocess development, although it has not been widely applied in industrial R&D. Here, an approach that offers a more time-efficient analytical platform is described that has the potential for a wider adoption of this technology in biopharma process development and optimisation.

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3. DETERMINATION OF THE RESIDANCE TIME DISTRIBUTION OF THE POLYMER-API MIXTURE DURING THE HOT MELT EXTRUSION PROCESS

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Hot melt extrusion (HME) is one of the technologies used for producing an amorphous form of API. It has been gaining in importance in recent years in pharmaceutical industry. However, one of the problems that arises during HME, which is performed at high temperatures, is the possible degradation of the API and /or polymer. Therefore, an important issue is to determine the influence of process parameters (screw rotation, feed rate, temperature etc.) on the residence time distribution of mixture polymer-API in the extruder, where it is exposed to high temperatures.

Determination of residence time distribution has been done with color tracer added to the formulation. During the processing small amount of tracer has been added into the extruder and the extrusion process was carried out. The HME was repeated with different process parameters obtaining series of samples. After processing, the photos of prepared samples were collected and based on the picture analysis the residence time distribution function was determined. Later, this methodology allows to connect the residence time distribution with HME process parameters. The results obtained during the investigation may allow to relate API degradation during the processing to process parameters and residence time distribution.

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4. PHARMACEUTICAL AND CHEMICAL INDUSTRY – DIFFERENT PROCESS APPROACH

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The paper focuses on differences between chemical and pharmaceutical approach to production and design of installations. Both industries use the same processes, i.e., crystallisation, mixing, distillation, filtration, drying, but usually the production scale is not the same, and both face the same problems, i.e., scaling-up.
The paper presents different ways of designing process installations, including materials used for the construction of apparatus and pipelines, and cleaning issues, which is extremely important in the pharmaceutical industry. The last one is the most important difference that has a huge impact on the selection of equipment (i.e., impeller type, shape of the baffles, and their number in process reactors) and the construction of the installation. This requires the use of a proper construction of the equipment that facilitates its cleaning or a proper course of installation to eliminate points that hinder the cleaning of the installation.

Another analysed issue is the appropriate selection of heating/cooling systems. They can guarantee adequate control of the process temperature, especially in the case of unexpected events.

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5. PROCESS ANALYTICAL TECHNOLOGIES (PATS) IN THE PROCESS IDENTIFICATION

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Research and innovation activities are aligned to WP1 and focused mainly on development of new process analytical technologies (PATs) with the particular interest of using them in process identification. At the beginning, theoretical and experimental knowledge about using the FBRM, PVM, and EasyViewer was introduced. Then, the crystallization experiments using an EasyMax reactor and an Easy Viewer were performed in cooperation with colleagues from the APC Innovation team. ORBIS secondee helped set up the experiment using automated lab reactor (EasyMax) in which also the EasyViewer 100 and EasyViewer 400 are brand new PAT tools (still in development) were applied. During the secodment the different tools of the Dynochem program were used to understand the process and quickly develop a scalable, robust unit quickly with reduced experimentation and improved collaboration. In particular, mixing and heat transfer was used to ensure adequate mixing and heat transfer on scale, using Easy or Optimax vessel database. Therefore, the ORBIS secondee, took part in on-line training concerning the prediction of solubility and selection of solvent using the Dynochem program. These tools and technologies will support ongoing research into API crystallization and process development and optimization activities.

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6. ORALLY DISINTEGRATING TABLETS WITH CANNABIDIOL IN THE CO-CRYSTAL FORM

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Cannabidiol (CBD) is poorly soluble active component of Cannabis spp. The co-crystallization method was used to increase the solubility of the parent compound (CBD). The 7 potential conformers and 2 different methods to obtain CBD cocrystals was tested. CBD cocrystals were successfully obtained with tetrahydropyrazine (THP) and L-proline by two separate techniques (ball milling and co-crystallization in methanol solution). The identification of the obtained structures was confirmed by technique X-Ray Powder Diffraction (XRPD). The solubility of CBD from the obtained binary system was determined. The dissolution of the binary obtained systems in artificial gastric juice and phosphate buffer at pH = 6.8 with the addition of surfactant (0,2% SDS) was determined. The physical stability of CBD cocrystals with L-proline was confirmed by the XRPD method. Orally disintegrating tablets containing cannabidiol and CBD in the co-crystal form was prepared. The dissolution of CBD cocrystals from oral formulations was increased.

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7. THE IMPORTANCE OF THE QUALITY CONTROL OF THE PREFORMULATION SUBSTRATES

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The substrates for drug production must meet the highest standards of the quality control to give the product of desired activity. For this purpose, it is important to thoroughly check their composition. The chosen methods must enable desired level of sensitivity and ability to determine characteristic impurities at a low level, providing fast and accurate results and follow the strict guidelines of the European Pharmacopoeia (Ph. Eur.).

Within the performed experiments the composition of the substrate delivered by the external company was tested (Milk thistle extract) including impurities characteristic and active substance detection and compared with the composition of the final product. Using the HLPC analysis, an in-depth study of the sylimarin content as well as related compounds (silicristin, silidianin, silymarin A, silymarin B, isosilymarin A, and isosilymarin B) were undertaken. Moreover, the substrate was tested using two analytical protocols, according to Ph. Eur. The results of this study show importance of frequent and accurate control of the APIs, impurities, and other relevant substances in pharmaceutical products. Application of various analytical and bioanalytical techniques must meet the standards of GMP and European Pharmacopoeia or other agencies responsible for drugs regulation and approval.

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8. COMPATIBILITY STUDIES OF THE API AND EXCIPIENTS (IN THE DRUG FORMULATION) WITH THE USE OF NOVEL TECHNOLOGICAL APPROACHES

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Almost every form of the drug consists of the basic components – active ingredient(s) and excipients. An active substance produces a biological effect in a living organism. An excipient is a chemical compound that is used to give the drug formulation the desired form. Such substances can be of natural or synthetic origins. They have a wide variety of physical and chemical properties that help form the right drug form.

The main difference between the active substance and the excipient is the fact that the excipient in the amounts used in a given drug cannot exert its own pharmacological effect. It can also not interact and adverse reactions that could affect the stability of the drug. Thus, only the active substance is the part of the drug responsible for changing the patient's condition (producing a therapeutic, prophylactic or diagnostic effect).

The main research aim was to analyze the influence of excipients on the chemical stability of drug formulation and the impact on the possibility of its production. Moreover, we made an attempt to find the compatible excipients from degradation and process ability points of view, with the use of novel technological approaches – Gamlen D1000 tableting instrument and MODDE® Design of Experiment Software.

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Work package 2 (WP2)

9. APPLICATION OF MORPHOLINE DERIVATIVES AS SKIN PERMEATION ENHANCERS IN COMBINATION WITH THERAPEUTICAL SYSTEMS

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From a fundamental perspective, transdermal drug delivery has always been limited by the skin's rigid and lipid-rich outer layer known as the stratum corneum (SC). For their ability to overcome this barrier, transdermal patches are becoming more and more popular also for their non-invasive character and easy self-administration by the patient. To adjust the adhesion performance, flexibility or stability of the patch, or to increase the solubility or permeability of the API, additives such as plasticizers, solubilizers or penetration enhancers may be added to the product. Penetration enhancers are compounds that can increase the permeability of the skin by altering the skin barrier properties and facilitating the entry of the drug into the bloodstream. Although many different structures interacting with the SC have been evaluated for their ability to enhance the drug permeation via the skin, only a few compounds meet all the qualitative demands. For this reason, we investigated a series of new *N*-alkylmorpholines with various side chains, then we incorporated the most effective ones to the form of transdermal patches using two different types of pressure sensitive adhesive as a patches matrix and we observed the effectivity of this combination in topical delivery of diclofenac sodium.

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10. IMIQUIMOD NANOCRYSTAL FOR IMPROVED DERMAL DRUG DELIVERY

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The immunostimulating agent imiquimod plays a key role in the treatment of (pre)cancerous skin conditions. Unfortunately, the high bioavailability of imiquimod delivered via standard formulations (e.g. imiquimod dispersion in gel or cream) is very questionable. Oral administration is also impossible due to the increased concentration of cytokines in the bloodstream after low doses. For these reasons, targeted topical delivery of imiquimod in nanocrystal (NC) form is an option to decrease its systemic side effects. NCs were prepared by wet milling method. NCs showed a uniform size about 120 nm and stability for at least 3 months, with a minimal effect on skin disruption that was demonstrated on porcine skin. NCs found to be 3 times more efficient compared to commercially available cream. At the same time, low permeation through the skin was proved. Both these results point to better imiquimod targeting from our formulation against the commercial product. Finally, the NCs were incorporated into special microneedles patches prepared by Digital Light Processing (DLP) 3D printing method from biocompatible resin.

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11. SYNERGISTIC ANTITUMOR EFFECT OF LIPOSOMAL-BASED FORMULATIONS OF OLAPARIB AND TOPOTECAN IN PRIMARY EPITHELIAL OVARIAN CANCER CELLS

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Olaparib is a PARP inhibitor that induces synthetic lethality in tumors with deficient homologous recombination (HR) repair. Unfortunately, PARPi treatment exerts limited efficacy in treating patients without HR deficiency. To overcome these limitations, a combination therapy alongside DNA-damaging therapeutic is a promising solution. The study aimed to develop liposome formulations of olaparib and topotecan and evaluate the efficacy of their combination on primary EOC cells. We used cell models from healthy epithelial ovarian tissue, malignant ascites from the peritoneum area of the patients with ovarian carcinoma, four samples of clear-cell tumors, and an endometrioid primary ovarian cancer cell line (E1p). Neutral liposomes were prepared from egg phosphatidylcholine, cholesterol, and DSPE-PEG(2000) amine in a mole ratio of 51:44:5, respectively, using the ethanol injection method. The cell viability after 72 h treatment with a liposomal-based formulation of topotecan, olaparib, and a combination of both compounds was assessed using the MTT assay. The mode of interaction (synergy, antagonism, or additivity) was determined by calculating the combination index (CI) using the CompuSyn software program. For both tested drugs, we obtained a wide range of IC50 values. Nevertheless, the combination of studied compounds showed a synergistic antitumor effect at most of the selected concentrations.

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12. THE AMORPHOUS SOLID DISPERSION OF API/POLYMER PREPARED BY HOT MELT EXTRUSION METHOD

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In recent years, increasing interest in the Hot Melt Extrusion (HME) for drugs manufacture in the pharmaceutical industry is observed. The mentioned technique is an innovative and efficient process that involves dispersing of an Active Pharmaceutical Ingredient (API) in a molten polymer, and then extruding the resulting mixture. This technology is environmentally friendly, as it does not require the use of solvents (as in spray drying), where potential hydrolytic degradation pathways of an active ingredient can occur.

During the Secondment in Zentiva, my activity was focused on fabrication of oral drug delivery system by HME method. The formed products were expected to be characterized by similar composition and properties to drug delivery systems obtained by spray drying or commercial products. In the first stage, fabrication of an amorphous solid solution of selected API with selected polymer(s) and/or plasticizers, applying the HME method, was performed. Furthermore, obtained extrudates were characterized applying FTIR(ATR) spectroscopy, modulated differential scanning calorimetry (DSC), X-ray powder diffraction analysis (XRPD), and textural analysis.

The obtained results demonstrated high potential of HME method that can be applied to produce solid dispersions of the amorphous form of the drugs. What is more, mentioned method may positively affect the solubility and bioavailability of the API.

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13. DEVELOPMENT OF TRANSETHOSOMES FOR TRANSDERMAL DELIVERY OF THYMOQUINONE

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Among many transdermal drug delivery systems transethosomes offer the advantages of liposomes and ethosomes. The presence of edge activators in addition to phospholipid, ethanol, and water makes transethosomes deformable and flexible which affects permeation through the skin. This study aimed in developing transethosomes for the transdermal delivery of thymoquinone.

Based on Langmuir monolayer studies, several lipid-surfactant pairs were investigated to optimize the interfacial and rheological properties of the formulation. Anionic, non-ionic, and mixed surfactants were used. The most promising results were obtained for the mixtures of anionic and non-ionic surfactants which can be explained by the synergistic intermolecular interactions. The best combinations were selected to prepare transethosomes for transdermal delivery of thymoquinone. The formulations were characterized in terms of vesicular size and zeta potential. A series of *in vitro* permeability tests (IVPT) were performed in Franz diffusion cells using human skin. The results confirmed the highest permeation rate for the formulation with the mixture of surfactants used as edge activators. All the formulations showed a very high entrapment efficiency and safety profile.

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14. SELF-EMULSIFYING SYSTEMS FOR DELIVERY OF LOW SOLUBLE ACTIVE PHARMACEUTICAL INGREDIENTS

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Low solubility in aqueous solutions is very often a limiting factor in the bioavailability of many pharmaceuticals. For efficient delivery of such substances, one effective solution is the use of self-emulsifying systems (SEDDS). However, for any new pharmaceutical, composing an optimal SEDDS formulation (including surfactant and co-surfactant concentration) is a major challenge. Based on design of experiment (DoE), a number of SEDDS mixtures differing in composition were created and characterized from the perspective of emulsion formation in aqueous solution and API solubility in them. A series of dissolution experiments were performed with the most optimal mixtures, which confirmed the high rate of drug release from the emulsion, which opens up great possibilities for the use of the designed SEDDS in the pharmaceutical industry.

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15. RHEOLOGICAL PROPERTIES AND ACYCLOVIR RELEASE PROFILE OF VARIOUS SEMISOLID PREPARATIONS

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The semisolid preparations development includes addressing a set of interrelated tasks: ensuring the optimal rheological properties of the system combined with required release rate of APIs.

During the internship, the rheological properties (viscosity, storage and loss moduli) of ten semi-solid formulations (creams, ointments, gels) differing in the quantitative and qualitative composition of surfactants and structurants were studied. Rotational and oscillatory rheological tests were performed on Rheometer Anton Paar FT-A-VMT-02, Cone-plate measuring system CP50-2.

The Drug Release Rate from semi-solid preparations using a Cell Apparatus (according to USP (1724)) was also determined.

Taking into account the lower bioavailability of the suspended API, the aim of the Drug Release Study was to characterize three semisolid formulations with suspended acyclovir with different compositions of emulsifiers and structuring agents. The studies of Drug Release Profile were performed on Franz's cell with the Sartorius cellulose acetate artificial membranes.

As a result, the data of comparative studies of rheological properties and Drug Release Profile of three formulations with suspended acyclovir are presented. The studies revealed a significant effect of the type and amount of emulsifiers and structuring agents on the rheological properties and Drug Release Profile from semisolid formulations with suspended API.

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16. FORMULATION AND CHARACTERIZATION OF LIPID NANOPARTICLES WITH POORLY WATER-SOLUBLE DRUG

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Lipid nanoparticles (LNPs) are a class of drug delivery systems that have gained increasing interest in the pharmaceutical industry due to their ability to efficiently incorporate and deliver poorly water-soluble drugs to target cells. LNPs are composed of biocompatible lipids and can be tailored to achieve specific drug release profiles and improve drug bioavailability. They have shown promise in the treatment of various diseases, including cancer, genetic disorders, and viral infections. LNPs have been approved in the recent years by the US Food and Drug Administration and the European Medicines Agency for the delivery of RNA-based therapeutics, such as mRNA vaccines against COVID-19.

The aim of this research work is to develop a formulation of lipid nanoparticles with a model drug and to evaluate its physical properties relevant for its therapeutic application.

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17. APPLICATION OF DOE STATISTICAL METHODS IN THE QBD APPROACH IN THE DEVELOPMENT OF INNOVATIVE ACTIVE SUBSTANCES AND MEDICINAL PRODUCTS

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Implementation of Quality by Design (QbD) by the FDA and ICH has caused a revolution in the manufacturing of medicinal substances and products. Originally, QbD methodology focused on the development of pharmaceutical manufacturing, but it has also been implemented for the analytical methods and is called Analytical Quality by Design (AQbD). Design of experiment (DoE) approach has a key role in the QbD concept. DoE is a specific method of modelling the examined processes and statistical analysis of measurement data. The use of DoE allows for obtaining the maximum information with minimum time and an economical budget. The purpose of the DoE is to define the design space, i.e. such variable ranges that guarantee the highest quality of optimized process parameters, test methods, products, etc.

The work presents the application of statistical methods of DoE and QbD approach in various areas of development of innovative active substances and medicinal products including screening of potential drug candidates, process development of API manufacturing, pre-formulation studies and process development of final dosage form as well as analytical methods optimization.

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18. VARIOUS APPROACHES FOR SOLUBILITY IMPROVEMENT OF POORLY WATER-SOLUBLE COMPOUND

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Development of many drugs is dealing with issues, mainly related to poor water solubility which is leading to low oral bioavailability. This class of drugs is assigned to the II or IV class of the Biopharmaceutical Classification System (BCS).

Approaches, used for the improvement in the solubility can be: (1) amorphization, to create a supersaturated solution by adsorbing onto a porous carrier; (2) spray drying and (3) holt-melt extrusion, to stabilize supersaturated conditions with polymers; (4) mixing with surfactants, to increase wettability or solubility; or (5) nanocrystals.

One of the very poor water-soluble drug candidates is compound belonging to BCS II created in Celon Pharma S.A. This research aimed to discover and compare different approaches for increasing solubility of this compound. They were compared mostly for their ability to ensure amorphous state, which was measured by X-ray powder diffraction. Subsequently dissolution tests were performed to observe release kinetics.

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19. CHARACTERIZATION OF COMPACTION PROPERTIES AND WETTABILITY OF HME MATERIALS DIFFERING IN PARTICLE SIZE

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Powder compression is a critical process in the manufacturing of the tablet dosage form. The contribution of the different microprocesses during compression are dependent on the mechanical and structural properties of the materials, such as their compaction behaviour, particle size and morphology as well as applied compression stress. Therefore, the initial particle size is one of the crucial parameter which needs to be considered during development of tableting process. The effect of particle properties on powder compressibility is complex since the particle are firstly re-arranged followed by their deformation and/or fragmentation. Moreover, the relative humidity during tabletting process and the moisture content in input materials can also affect the compression behaviour.

In our study, the impact of initial particle size on powder compaction has been investigated for HME materials containing Kollidon VA 64 and the selected API. The obtained results have shown that the initial size of particles has an impact on the tensile fracture stress of HME material. Smaller particles formed more harder compacts than those from the larger particles even though the solid fraction parameter was similar. The applied humidity stress for the studied powders significantly changed the compaction behaviour: we observed an interesting phenomenon that tensile fracture stress increased for the tablets made of smaller particles whereas it increased for the compacts made of larger particles. The wettability of the formed compacts were determined by contact angle measurement. The extrudates are hydrophilic.

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20. INVESTIGATION OF A SELECTED LOW MOLECULAR WEIGHT COMPOUND AS A POTENTIAL PLASTICIZER IN THE HME PROCESS

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The application of HME expanded to the pharmaceutical industry at the beginning of the 1970s and was used in formulation and product development as well as manufacturing. From that time the use of this method has continued to gain in importance, since it allows obtaining an amorphous solid dispersion of a pharmaceutically active ingredient (API), usually slightly soluble in water, in a matrix of a suitable polymer(s). HME is performed at high temperature and it is important to select the process parameters so that material degradation does not occur. The addition of API often contributes positively to lowering the glass transition temperature of the polymer, but this decrease is not always sufficient. Therefore, in order to lower the processing temperature plasticizers are often added.

The possibility of using a low molecular weight compound (LMWC) with potential plasticizing properties in the HME process was investigated. The influence of LMWC on the course of the extrusion process and the possibility of obtaining a solid API dispersion in the polymer matrix were examined. Addition of 5 wt.% of LMWC allowed to significantly reduce the extrusion temperature and to obtain an amorphous solid polymer-API dispersion.

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21. CHARACTERISATION OF PALIPERIDONE PALMITATE NANOSUSPENSIONS WITH TIME-GATED AND COHERENT RAMAN SPECTROSCOPIES

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Paliperidone palmitate nanosuspensions are long-release parenteral drug formulations used to treat schizophrenia. It is important to have suitable tools to characterize the nanosuspension including particle, size and morphology as well as solid-state. Before this study, conventional characterization methods including IR spectroscopy, X-ray powder diffraction and dynamic light scattering were used. Since paliperidone palmitate does not fluoresce, suspension nanoparticles can also be analyzed by Raman spectroscopy. Raman spectroscopy is a versatile label-free, chemically and solid-state specific technique for monitoring possible changes in solid-state structure and also allowing visualization of non-fluorescent nanoparticles in and around cells. Therefore, the goals of our work were to 1) characterize paliperidone palmitate nanosuspensions by using two variants of Raman spectroscopy, namely time-gated and coherent Raman spectroscopy, 2) compare different formulations, and 3) to evaluate the capability of coherent Raman microscopy to study the nanoparticle-cell interactions.

Materials used in the study were excipients from the formulation with the API paliperidone palmitate, formulations with different API particle size distributions (native suspension and samples that were previously centrifuged and then precipitate was dried under 30 ^{0}C). Time-gated Raman spectroscopy (Timegate Instruments, Oulu, Finland) was used for characterization of the excipients, native nanosuspensions and dried nanosuspensions.
The initial results revealed that excipients and drug resulted in distinctive Raman signals and thus coherent Raman microscopy could be used as a rapid and label-free imaging method to further characterize the materials. Individual nanoparticles could be imaged, the spectra could be compared and conclusions about formulation similarity could be drawn. The obtained spectra of nanocrystals corresponded to that of paliperidone palmitate. Overall, the study confirmed that Raman spectroscopy and coherent Raman microscopy are excellent tools to characterize and visualize nanocrystals. The next step in the research would be to analyze morphology and interaction between nanosuspension and cells by using coherent Raman microscopy.

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22. THE CONTEST OF NANOPARTICLES: SEARCHING FOR THE MOST EFFECTIVE TOPICAL DELIVERY OF CORTICOSTEROIDS

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Owing to their complicated pathophysiology, the treatment of skin diseases necessitates a complex approach. Conventional treatment using topical corticosteroids often results in low effectiveness and the incidence of local or even systemic side effects. Nanoformulation of potent anti-inflammatory drugs has been selected as an optimal strategy for enhanced topical delivery of corticosteroids. In order to assess the efficiency of various nanoformulations, we formulated hydrocortisone (HC) and hydrocortisone-17-butyrate (HCB) into three different systems: lipid nanocapsules (LNC), polymeric nanoparticles (PNP), and ethosomes (ETZ). The systems were characterized using dynamic light scattering for their particle size and uniformity and the morphology of nanoparticles was observed by transmission electron microscopy. The nanosystems were tested using ex vivo full thickness porcine and human skin for the delivery of HC and HCB. The skin penetration was observed by confocal microscopy of fluorescently labelled nanosystems. ETZ were proposed as the most effective delivery system for both transdermal and dermal drug targeting but were also found to have a profound effect on the skin barrier with limited restoration. LNC and PNP were found to have significant effects in the dermal delivery of the actives with only minimal transdermal penetration, especially in case of HCB administration.

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23. DEFORMABLE LIPOSOMAL HYDROGEL FOR DERMAL AND TRANSDERMAL DELIVERY OF MELOXICAM

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Meloxicam (MX) is an anti-inflammatory and analgesic drug used in joint, bone and muscle pain and in the course of rheumatoid arthritis and osteoarthritis. It is also used in the short-term symptomatic treatment of exacerbations of rheumatoid diseases, such as: rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis. When taken orally, however, it can cause a number of side effects from the digestive system such as indigestion, nausea or vomiting, abdominal pain, constipation, flatulence and diarrhea. Therefore, it seems reasonable to search for alternative routes of MX administration, among which transdermal seems to be the most promising and safe.

In the present study, a poloxamer P407 based hydrogel system, containing various vesicular nanocarriers (liposomes, transfersomes and flavosomes), has been prepared as a potential therapeutic vehicle for topical delivery of MX.
First, the vesicles were characterized in terms of size, drug entrapment efficiency, zeta potential, and stability. Further, the MX-loaded carriers were incorporated into a poloxamer P407 gel and tested for rheological properties and stability. Also the *ex vivo* permeation across human cadaver skin was evaluated by both HPLC analysis and confocal laser scanning microscopy (CLSM).

It turned out that the developed deformable liposomes exhibited homogeneous sizes less than 120 nm with a higher entrapment efficiency as compared to conventional liposomes. Moreover, the deformable liposomal gel formulations showed improved permeability compared to a conventional liposomal gel and a liposome-free gel.
These deformable liposomal hydrogel formulations can be a promising alternative to conventional oral delivery of MX by topical administration. Notably, flavosome-loaded gel formulations displayed the highest permeability through the deeper layers of the skin and shortened lag time, indicating a potential faster on-site pain relief and anti-inflammatory effect.

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24. ASSESSMENT OF THE RELATIONSHIP BETWEEN TABLET MICROSTRUCTURE AND DISSOLUTION PERFORMANCE AIDED BY THE GHVC METHOD

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The performance of a pharmaceutical formulation, such as the drug (API) release rate is significantly influenced by the properties of the materials used, the composition of the final product and the tablet compression process parameters. However, in some cases, the knowledge of these input parameters does not necessarily provide a reliable description or prediction of tablet performance. Therefore, the knowledge of tablet microstructure is desirable to understand such formulations.

The specific cases can include a combination of materials with different deformability, for example, a combination of a firm and brittle excipient ($CaHPO_4 \cdot 2H_2O$) and an API formulated via hot-melt extrusion, usually of a fairly deformable nature. For the purpose of this work tablets containing such materials were prepared with the use of the gravitational-based high-velocity compaction (GHVC) method, which can provide more detailed information on the compression process influence on tablet microstructure creation, at a process speed much more similar to rotary tablet presses usually used in the industry. Subsequently, the tablet microstructure (quadratic mean of the equivalent diameter of the excipient domains on the tablet cross-section area) was evaluated via an image-based method using the SEM pictures and the API release rate was assessed with the use of a USP4 dissolution method. Based on the prepared tablet properties an area in the created design space was found where the tablet dissolution performance can be described based solely on the microstructural parameter, providing data for a broader model system useful in describing and solving problems in compressed solid dosage forms in which a plastic component is present and specific API release is required.

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25. INLINE TORQUE MEASUREMENT FOR END-POINT DETERMINATION OF HETEROGENEOUS FORMULATIONS IN HIGH-SHEAR WET GRANULATION

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Wet granulation, a widely used technique in solid dosage form manufacturing, poses challenges due to complex granulation mechanisms and their impact on intermediate and final product attributes. Power consumption or torque has been explored as a potential process monitoring tool during granulation. However, challenges such as interference and interpretation complications hindered its implementation.

This study aims to evaluate the feasibility of using torque measurements for granulation monitoring on high shear granulator, considering various formulation and process variations. The correlation between torque measurements and granule attributes such as particle size distribution (PSD) and porosity will also be investigated. The objectives include understanding granulation mechanisms, detecting the endpoint based on targeted dynamic median particle size (d50) range, and establishing correlations between torque, PSD, and porosity. The findings of this study will contribute to improving process monitoring and control in wet granulation, advancing pharmaceutical Quality-by-Design practices.

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Work package 3 (WP3)

26.SIMULTANEOUS QUANTIFICATION OF METRONIDAZOLE, CEFAZOLIN, AND CEFTRIAXONE BY UPLC-MS/MS

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Successful antimicrobial prophylaxis before surgeries depends on attaining the therapeutic drug concentration at target sites. Inadequate drug exposure might result in prophylaxis failure, higher surgical site infection rate, and increased antibiotic resistance. The biodisposition of antibiotics might differ in special populations (e.g., obese vs. lean patients). Little is known about how obesity may influence pharmacokinetics and if obese patients require a modified dosing strategy.

Therefore, a UPLC-MS/MS method was developed and validated to simultaneously measure metronidazole, ceftriaxone, and cefazolin in human plasma, adipose tissue, and intestinal tissue. The plasma sample preparation involved simple protein precipitation. Tissue samples required an additional filtration using Captiva EMR plates to remove lipid components. The chromatographic resolution was achieved using a Synergi Fusion-RP column (50 × 2 mm, 4 µm) and a mobile phase consisting of water and methanol (both containing 0.1% formic acid) at a flow rate of 0.5 mL/min. Detection and quantification were performed using electrospray ionization (positive mode) with multiple reaction monitoring. The method was validated according to the FDA guidelines. The method can be further applied for pharmacokinetic studies and therapeutic drug monitoring.

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27. THE DEVELOPMENT OF NEW DISSOLUTION MODEL USING PARAMETRIZATION OF NUMEROUS CONTRACTION FORCES WITH SMALL MAGNITUDE IN THE GASTROINTESTIONAL TRACT

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Biorelevant dissolution tests devices are already capable of simulating the mechanical and physicochemical conditions that affect dosage forms during their gastrointestinal passage. However, mimicking gastrointestinal tract conditions in biorelevant dissolution tests could be further optimized by applying the information from numerous contraction forces with small magnitude that occur in the gastrointestinal tract. The objective of this work is to apply these small magnitude contraction data in the development of new models for drug dissolution.

Longitudinal data of contraction forces (number and magnitude of signals) in the gastrointestinal tract in healthy fasting or fed subjects after ingestion of telemetric capsules (Smart pill) were previously collected. Signal processing methodology was used to parametrize the longitudinal data of small magnitude contractions. The results of this parametrization could be applied in the development new drug dissolution models.

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28. PHARMACOKINETIC MODELLING & SIMULATION – A BRIEF SUMMARY OF APPLICATIONS IN DRUG DEVELOPMENT

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Pharmacokinetic modelling & simulation are applied in development of both generic and innovative medicinal products. This interdisciplinary approach combines knowledge from pharmaceutical, medical, engineering and mathematical sciences. Main types of pharmacokinetic modelling & simulation include: (1) PBBM - physiologically based biopharmaceutics models; (2) PopPK – population pharmacokinetics; (3) PBPK - physiologically based pharmacokinetic analyses. They are well established for oral drug forms, but their application to topical and inhalation products is an emerging field.

Applications of pharmacokinetic modelling & simulation in drug development were summarized basing on literature data and personal experience. Key features of each type were listed.

It is expected that regulatory recommendations for model-informed drug development (MIDD) will grow in the future. Therefore, further developments in pharmacokinetic modelling & simulation are necessary.

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29. EVALUATING THE FOOD EFFECT FOR RIVAROXABAN WITH CUSTOM-BUILT IN-VIVO-IN-VITRO PREDICTION MODELS

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Rivaroxaban, a potent anticoagulant, is a poorly soluble drug that exhibits significant food effects. The drug's bioavailability under fasted conditions decreases considerably when the dose exceeds 10 mg, and greater strengths are recommended to be taken with food only. The aim of this study was to model and parametrize this food effect based on dissolution experiments conducted in media simulating gastrointestinal fluids.

The model was built using the data available for the originator – Xarelto. The function describing the dissolution was based on the modified Noyes-Whitney equation [1]. Dissolution parameters, z and saturated concentration (C_s), were used as input for the in-vitro-in-vivo prediction (IVIVP) model joint. The model included a multisegmental gastrointestinal tract and used physiological volumes, surface areas, and interindividual pharmacokinetic variability.

The model parameters were optimized to achieve exposure comparable with the literature data. It was shown that the expected effective permeability value should be within the 1 – 2 x 10^{-5} cm/s range. Sensitivity analysis revealed that C_s had the greatest impact on the simulated pharmacokinetic profiles. Also, additional interindividual variability allowed a more realistic approximation of the reported.

In conclusion, IVIVP models can help find key elements for understanding the drug in vivo performance.

[1] Takano R, et al. Oral absorption of poorly water-soluble drugs: computer simulation of fraction absorbed in humans from a miniscale dissolution test. Pharm Res. 2006 Jun;23(6):1144-56

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30. CONVENIENT LC-UV METHOD FOR DETERMINATION OF BUDESONIDE IN DIGESTED MILK AND FED STATE SIMULATED INTESTINAL FLUID

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The use of biorelevant media in dissolution testing of oral solid dosage forms significantly improves predicting in vivo performance of poorly water-soluble drugs. However, the presence of bile salts, phospholipids, and proteins in the media makes the drug quantification challenging. The aim of the study was to develop a convenient and rapid LC-UV method for determination of budesonide (BCS class II drug) in fed state media: cow milk digested with pepsin and pancreatin, and simulated intestinal fluid (FeSSIF). The milk samples spiked with budesonide were extracted and centrifuged to obtain a clear supernatant, while the FeSSIF samples were injected directly onto the LC column. Among the seven tested LC columns and four types of mobile phases, the best resolution of the budesonide epimers and media components was obtained with the Xterra Phenyl column and water-acetonitrile gradient elution. The developed method was validated according to the International Conference on Harmonization guidelines. The calibration curves were linear in the range of 0.4 - 12 mg/L. The method was specific, accurate (relative error <5%), and precise (coefficient of variation <4%). Therefore, the method can be used in dissolution testing of budesonide products at simulated postprandial conditions.

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31. INFLAMMATION MARKERS AND OXIDATIVE STRESS PARAMETERS IN RAT LUNGS FOLLOWING INHALATION OF SULFUR MUSTARD

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Pulmonary toxicity is responsible for most morbidity and mortality following sulfur mustard (SM) exposure. Understanding the pathogenesis of acute injury and the progression to chronic disease is important as there are currently no therapeutics to treat SM poisoning in victims exposed to this toxic vesicant. To test this, we developed a novel inhalation model in rats which provides direct delivery of SM vapor to the lung and airways.

SM vapor inhalation caused dose (0.2-0.6 mg/kg)-related damage to the respiratory tract within 3 days of exposure. Proinflammatory proteins receptor for advanced glycation end product (RAGE), high-mobility group box protein (HMGB)-1, and matrix metalloproteinase (MMP)-9 increased in a biphasic manner following SM inhalation, along with surfactant protein-D (SP-D). Tumor necrosis factor (TNF)- 〈 and inducible nitric oxide synthase (iNOS), inflammatory proteins implicated in mustard lung toxicity, and the proinflammatory/profibrotic protein, galectin (Gal)-3, were upregulated in alveolar macrophages and in bronchiolar regions at 3 and 28 days post-SM. Inflammatory changes in the lung were associated with oxidative stress, as reflected by increased expression of heme oxygenase (HO)-1.

These data demonstrate a similar pathologic response to inhaled SM in rats and humans suggesting that this rodent model can be used for mechanistic studies and for the identification of efficacious therapeutics for mitigating toxicity.

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32. CHALLENGES AND STRATEGIES IN LOADING HYDROPHOBIC ANTICANCER DRUG BEXAROTENE INTO EXOSOMES FOR TARGETED DRUG DELIVERY

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The preparation, loading, and characterization of exosomes as vehicles for drug delivery have become very important in biomedical research for targeted drug delivery. In this study, we focused on the preparation of exosomes, their loading with the hydrophobic anticancer drug bexarotene, and the challenges encountered in the development of this drug delivery system.

Exosomes were isolated from the HUT 78 cell line and loaded with bexarotene. Three different techniques were used for drug loading: Incubation at 37 °C, slow injection, and sonication. However, a major hurdle was determining the efficiency of drug loading. Bexarotene adhered strongly to plastic surfaces and filters, resulting in limited drug recovery (approximately 60%) and inconclusive results.

After extensive iterations, we finally employed the dialysis method, which allows accurate quantification of the active ingredient content through an indirect approach. In addition, we found that the most efficient method for bexarotene incorporation was slow injection into the exosome dispersion. Despite the high entrapment efficiency, in vitro results showed limited success, likely due to the low concentration of exosomes.

Further studies will investigate the potential of exosomes from different cell lines as drug carriers to determine which exosomes have the highest affinity for cancer cells.

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Work package 4 (WP4)

33.SMART WAY TO ADMINISTER HIGH DOSES OF A NEW DRUG CANDIDATE OF POOR SOLUBILITY VIA INHALATION ROUTE – SPRAY-DRYING IN DRY POWDER FORMULATION

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The inhalation route of administration of drug products uniquely challenges hydrophobic, poorly soluble active pharmaceutical ingredients (APIs), mostly due to limited liquid volume in the lungs (10-30mL). Solubility plays then a critical role in drug bioavailability. It is therefore essential to develop a proper formulation to overcome these problems and effectively deliver such compounds to the lungs.

Our work focuses on the development of a dry powder formulation containing an innovative API with anti-fibrotic activity. Jet milling technology was previously used to obtain an inhalable fraction of mentioned ingredient, but poor solubility and flowability of obtained inhalable crystalline fraction were observed. These factors constitute a significant drawback for implementing jet-milling technology to produce an appropriate grade of studied API during dry powder formulation development.

Deployment of spray-drying technology allowed for the production of stable amorphous powder with an inhalable fraction of proper particle size distribution. Particle morphology using scanning electron microscopy (SEM), stability of amorphous form using the X-ray method and aerodynamic properties using Next Generation Impactor (NGI) are measured to confirm the properties of the innovative spray-dried compound.

Spray-drying technology is expected to be an excellent alternative to jet-milling technology in developing formulations with this new drug candidate.

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34. MICROSCALE POWDER FLOWABILITY:

A NOVEL METHOD. ADVANTAGES AND APPLICATIONS.

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Microscale flowability analysis is a powerful tool to understand the underlying mechanisms that govern powder flow. This is particularly relevant for industrial applications such as die filling during the manufacture of oral solid dosage forms (OSD), where particle-level behaviour dominates over bulk behaviour. In this context, we present a novel image-based method of powder flow through an orifice, with a special emphasis on process optimization and formulation design. We discuss the impact of material attributes and process parameters on flowability and compare with state-of-the-art flow measurement techniques such as powder rheometry.

The method significantly increases the sensitivity to cohesive phenomena, especially for powders with low levels of bulk cohesion. The lower stress measuring setup allows for improved measurement of neglected weak attractive van der Waals forces. Image analysis applied to powder flow analysis provides benefits beyond visualization and communication of results, including increased measurement speed and simultaneous physical characterization of particles.

The knowledge gained from microscale flow analysis is applied to improve product quality and reduce manufacturing costs. Our findings will be discussed in detail during the conference, highlighting the advantages and applications of the method and its potential impact on the pharmaceutical industry.

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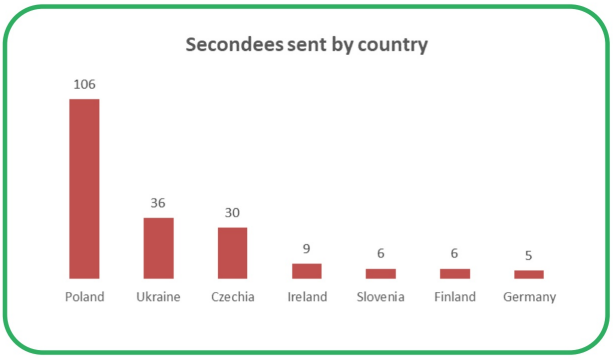
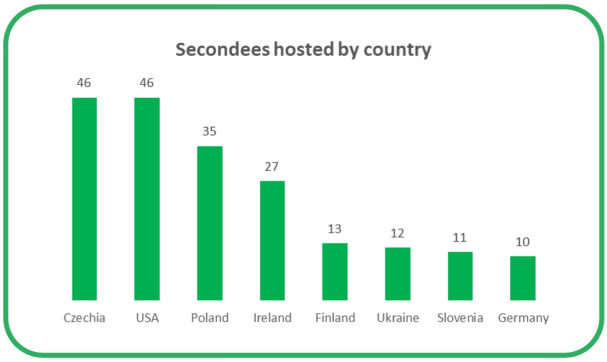
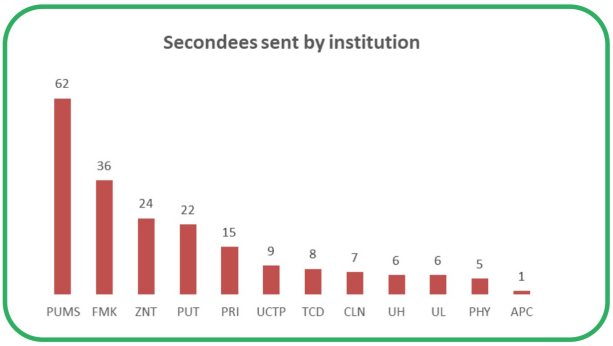
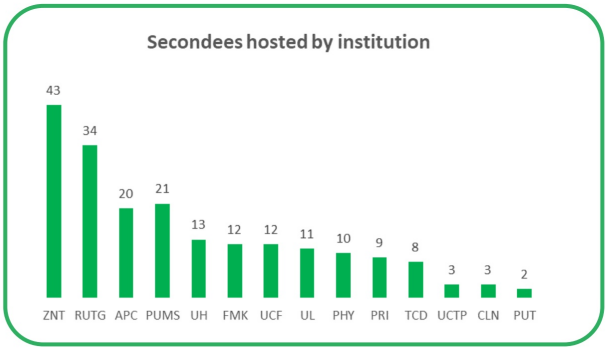
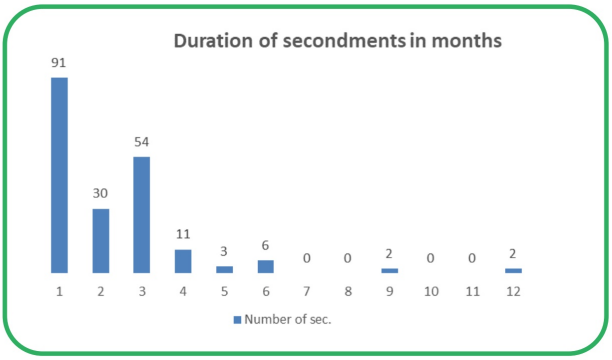
TOTAL BUDGET: 2 268 000 €

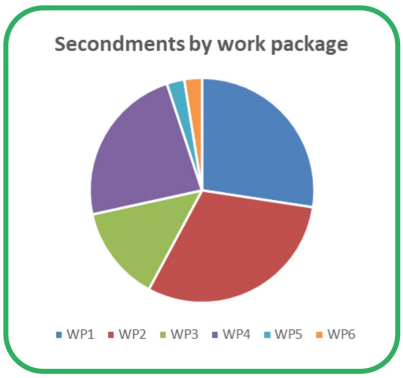












COORDINATOR

PUMS- POZNAN UNIVERSITY OF MEDICAL SCIENCES

BENEFICIARIES

FMK - JSC FARMAK (UKRAINE)
TCD - TRINITY COLLEGE DUBLIN (IRELAND)
PRI - LUKASIEWICZ RESEARCH NETWORK - PHARMACEUTICAL RESEARCH INSTITUTE (POLAND)- Terminated
PHY - PHYSIOLUTION GMBH (GERMANY)
APC - APPLIED PROCESS COMPANY LIMITED (IRELAND)
UH - UNIVERSITY OF HELSINKI (FINLAND)
ZNT - ZENTIVA, K.S. (CZECHIA)
PUT - POZNAN UNIVERSITY OF TECHNOLOGY (POLAND)
UL - UNIVERSITY OF LJUBLJANA (SLOVENIA)
UCTP - UNIVERSITY OF CHEMISTRY AND TECHNOLOGY IN PRAGUE (CZECHIA)
CLN - CELON PHARMA S.A. (POLAND)

PARTNERS

RUTG - RUTGERS UNIVERSITY (USA)
UCF - UNIVERSITY OF CENTRAL FLORIDA (USA)

Prepared by: Piotr Gadziński, Julia Krysztofiak, Maciej Michalak, Emilia Jakubowska, Katarzyna Filip

The ORBIS Project has received funding from the European Union's Horizon 2020 Research and Innovation Programme under the Maria Sklodowska-Curie Action: Grant Agreement No 778051

ORBIS timeline

ORBIS
FINAL CONFERENCE
POZNAŃ, JULY 5TH-6TH 2023

Idea of Consortium 2014- 2015
(Dr Piotr RUDZKI and Dr Bartłomiej MILANOWSKI)

September 2015 — **Acceptation of PUMS as Grant Coordinator**

January 2016 — **Consortium established**

17.09.2017 — **Consortium Agreement signed by all beneficiaries:**
- Pharmaceutical Research Institute (PRI,PL),
- Trinity College Dublin (TCD, IRL),
- APC Ltd (APC, IRL),
- University of Helsinki (UH, FIN),
- Physiolution GmbH (PHY, GER),
- Zentiva (ZNT, CZ), Farmak JSC (FMK, UA)

05.10.2017 — **Grant Agreement Signed by all Beneficiaries**

26.03.2018 — **Partnership Agreement signed by:**
- Rutgers University (RUTG, USA)
- Poznań University of Medical Sciences (PUMS,PL)
- Pharmaceutical Research Institute (PRI,PL)
- Farmak JSC (FMK, UA)

before 1.03.2018 — **ETHICS ADVISORY BOARD** established

12-13.04.2018 — **Kickoff Meeting, Poznań**

17.04.2018 — **First secondment - Michał Falkowski from PUMS stayed 3 months in Zentiva**

24.07.2018 — **ORBIS - Networking Event PUT / PUMS / PRI**

27.05-26.06.2018 — **Coordinator first secondment in USA, Rutgers**

July 2018 — **ORBIS secondees from PUMS and PRI with Sharon Davin at APC**

15.11.2018 — **ORBIS managing team members and the Coordinator at Multidisciplinary Conference on Drug Research in Warsaw**

21.09.2018 — **Post-secondment Seminar Pharmaceutical Research Institute, Warsaw (PRI/PUMS)**

12-14.06.2019 — **1st ORBIS Summer School and Workshops on Pharmaceutical Preformulation and Processing, Dublin**

11.02.2019 — **1st ORBIS research article published**

18-20.09.2019 — **2nd ORBIS Summer School on Oral Dosage Forms: Fundamentals, Challanges and Future Oppurtinities and ORBIS Workshop on Dosage Forms and Drug Delivery Systems, Helsinki**

26.09.2019 — **Mid-term Meeting (MtM), Poznań**
- To assess the general advancement of the project
- To identify issues related to project implementation
- To find the relevant solutions
- To meet researchers seconded in the project

COVID-19

Suspension of the project due to the CoVID-19 pandemic **from March 2020 to October 2021**

24.02.2022 — **Outbreak of war in Ukraine**

7-8.09.2022 — **4rd ORBIS Summer Schoolon biopharmaceuticalevaluation of dosage forms and drug delivery**

20-22.06.2022 — **3rd ORBIS Summer School on topical and transdermal drug delivery systems, Poznań**

Final Conference 5-6th of July 2023 POZNAŃ
Final Meeting 7th of July 2023 POZNAŃ

Prepared by: Piotr Gadziński, Antoni Białek, Julia Krysztofiak

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Not only Secondments...

ORBIS Summer Schools & Workshops

ORBIS FINAL CONFERENCE POZNAŃ, JULY 5-6TH 2023

Dublin, Ireland

Organizers: Trinity College Dublin, APC, Farmak

1st Summer School

on pharmaceutical preformulation testing of APIs and dosage forms

When: 12-13th June 2019 Number of participants: 52

Topics:

- solid state pharmaceutical materials (amorphous, liquid crystalline and cocrystalline)
- continuous processing
- fundamentals and application of preformulation and characterisation
- Process Analytical Technologies

Open Workshop

on process development of drug substances

When: 14th June 2019 Number of participants: 50

- practical approaches and real cases established at GMP manufacturing facility
- API process development
- validation, transfer of technologies from laboratory to pilot and industrial scale for solid dosage forms

Representatives from Farmak contributing to the workshop and the ORBIS project coordinator, Prof. Janina Lulek

Helsinki, Finland

Organizers: University of Helsinki, Zentiva

2nd Summer School

on oral dosage and drug delivery systems

When: 18-19th September 2019 Number of participants: 75

Topics:

- challenges and perspectives in development of oral dosage forms
- advanced emerging technologies: nano- and microparticles, minitablets and mesoporous materials

Lively discussion during the poster session.

Open Workshop

on dosage form and drug delivery systems

When: 20th September 2019 Number of participants: 18

Hands on demonstrations:

- spray drying for development of microparticles
- compression of minitablets
- coherent anti-Stokes Raman spectroscopy (CARS) in drug characterization

Poznań, Poland

Organizers: Poznan University of Medical Sciences, Rutgers University

3rd Summer School

on topical and transdermal drug delivery systems

When: 20th-22nd June 2022 Number of participants: 67

Topics:

- various aspects of topical and transdermal delivery of drugs
- state of the art and recent progress in the development of topical and transdermal delivery systems (e.g. microemulsions, transdermal patches, microneedles)
- Characterization methods for topical dosage forms

Practical demonstrations:

- *In vitro* permeation/release testing of dermal and transdermal dosage forms (USP IV, Franz diffusion cells)
- Texture analysis of semisolid preparations

Prague, Czech Republic

Organizers: Zentiva, Phytiolution, University of Chemistry and Technology Prague

4th Summer School

on biopharmaceutical evaluation of dosage forms and drug delivery

When: 7-8th September 2022 Number of participants: 76

Topics:

- state of the art and the most recent progress within the area of biopharmaceutical evaluation of dosage forms
- biopharmaceutical principles and novel techniques, drug delivery systems of increased bioavailability,
- in vitro/in vivo relationship,
- bioanalytical methods and non-traditional routes of absorption

Martin Baluch receiving the Best Poster Award

Open Workshop

on biopharmaceutical evaluation of dosage forms and drug delivery

When: 9th September 2022 Number of participants:45

Practical sessions:

- novel dissolution methods
- dissolution imaging
- in situ analytical techniques
- computational bioanalytical tools

Prepared by Emilia Jakubowska, Dorota Danielak

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ORBIS Beneficiaries and Partners

FINAL CONFERENCE
POZNAŃ, JULY 5TH-6TH 2023

APC

APC Ltd.
Power up your process development knowledge
Beneficiary, Non-Academic, EU,
Established 2011, ORBIS 2018-2023

UNIVERSITY OF HELSINKI

Helsingin Yliopisto
International top-level pharmaceutical research with the seamless combination of high-level education and advanced business collaboration
Beneficiary, Academic, EU,
Established 1640, ORBIS 2018-2023

POZNAN UNIVERSITY OF TECHNOLOGY

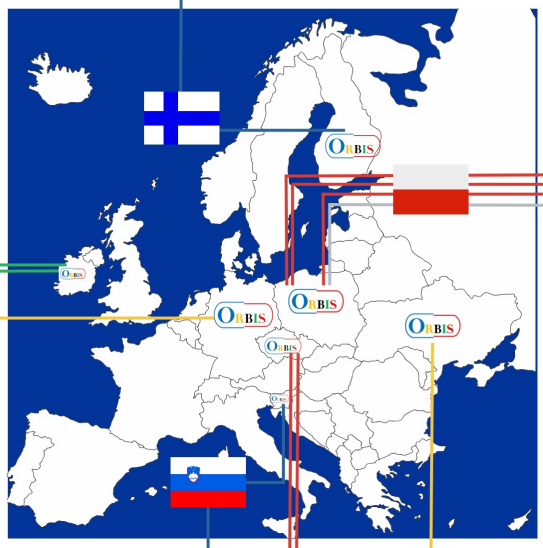
Politechnika Poznańska
Unity of goals – variety of possibilities
Beneficiary, Academic, EU,
Established 1919, ORBIS 2019-2023

POZNAN UNIVERSITY OF MEDICAL SCIENCES

Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu
Where knowledge & practice come together
Coordinator, Academic, EU,
Established 1918, ORBIS 2018-2023

TRINITY COLLEGE DUBLIN

Coláiste na Tríonóide, Baile Átha Cliath
Embracing the past, looking to the future
Beneficiary, Non-Academic, EU,
Established 1529, ORBIS 2018-2023



CELON PHARMA

Celon Pharma S.A.
Shape the future of healthcare
Beneficiary, Non-Academic, EU,
Established 2002, ORBIS 2021-2023

PHYSIOLUTION

Physiolution GmbH
Predictive dissolution testing
Beneficiary, Non-Academic, SME, EU,
Established 2009, ORBIS 2018-2023

PHARMACEUTICAL RESEARCH INSTITUTE

Instytut Farmaceutyczny
Forming cooperation between the pharmaceutical industry and the scientific community to improve modern medicines for the patients
Beneficiary, Academic, EU,
1952-2020, ORBIS 2018-2020

UNIVERSITY OF CHEMISTRY AND TECHNOLOGY IN PRAGUE

Vysoká Škola Chemicko-Technologická v Praze
International top-level pharmaceutical research with the seamless combination of high-level education and advanced business collaboration.
Beneficiary, Academic, EU,
Established 1807, ORBIS 2021-2023

FARMAK

JSC «Farmak»
Ukrainian manufacturer of medicines to European standards
Beneficiary, Non-Academic, Associated country,
Established 1925, ORBIS 2018-2023

UNIVERSITY OF LJUBLJANA

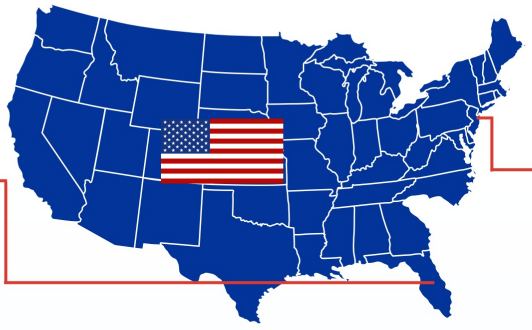
Univerza v Ljubljani
Continuously and creatively contribute to the quality of life
Beneficiary, Academic, EU,
Established 1919, ORBIS 2021-2023

ZENTIVA

Zentiva
At Zentiva, we are united on our common purpose to ensure the supply of high-quality and affordable medicines to the people who depend on our products every day
Beneficiary, Non-Academic, EU,
Established 1488, ORBIS 2018-2023

UNIVERSITY OF CENTRAL FLORIDA

Unleashing the potential within every individual, enriching the human experience through inclusion, discovery and innovation, and propelling broad-based prosperity for the many communities we serve
Partner, Academic, Third country,
Established 1963, ORBIS 2021-2023



RUTGERS

Rutgers, The State University of New Jersey Sol iustitiae et occidentem illustra
Partner, Academic, Third country,
Established 1766, ORBIS 2018-2023

Prepared by: Piotr J. Rudzki, Anna Froelich, Antoni Białek, Maciej Michalak

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ORBIS Management-
Navigating the unforeseen challenges in a large EU programme

ORBIS FINAL CONFERENCE
POZNAŃ, JULY 5-6TH 2023

ORBIS, when it received funding in 2018, was the second largest RISE award in the EU programme. Naturally, changes can happen in a large 4-year award and the Project Coordinator, Leads and Committees were tasked with both running of the programme (as outlined below) and managing risk. A change in a beneficiary member status, a pause due to a global pandemic and some enforced restrictions due to the ongoing war in Ukraine could not stop ORBIS. Instead, the management team created opportunities and solutions- and today, the team is a 13-member strong consortium who have successfully delivered on the programme goals and deliverables.

Management, Leadership & Committees

Management Purpose and Scope:

- To assess the general advancement of the project
- To identify & resolve issues related to project implementation
- To coordinate research secondments
- To manage financial administration

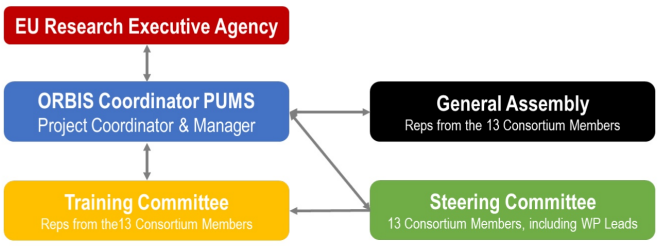
Scientific and technical WP Leadership

WP1	WP2	WP3
Drug Substances and pharmaceutical preformulation	Dosage Forms and Drug Delivery Systems	Biopharmaceutical evaluation of dosage forms and drug delivery systems
Lead Lidia Tajber, TCD Stane Srčič, UL	**Lead** Anne Juppo, UH Alexsandra Dumicic, ZNT	**Lead** Grzegorz Garbacz, PHY Marta Karażniewicz-Łada PUMS
Co-Lead UH, PUMS, FMK, ZNT	**Co-Lead** PUMS, FMK, UCTP	**Co-Lead** ZNT, FMK, PUMS

WP Leadership

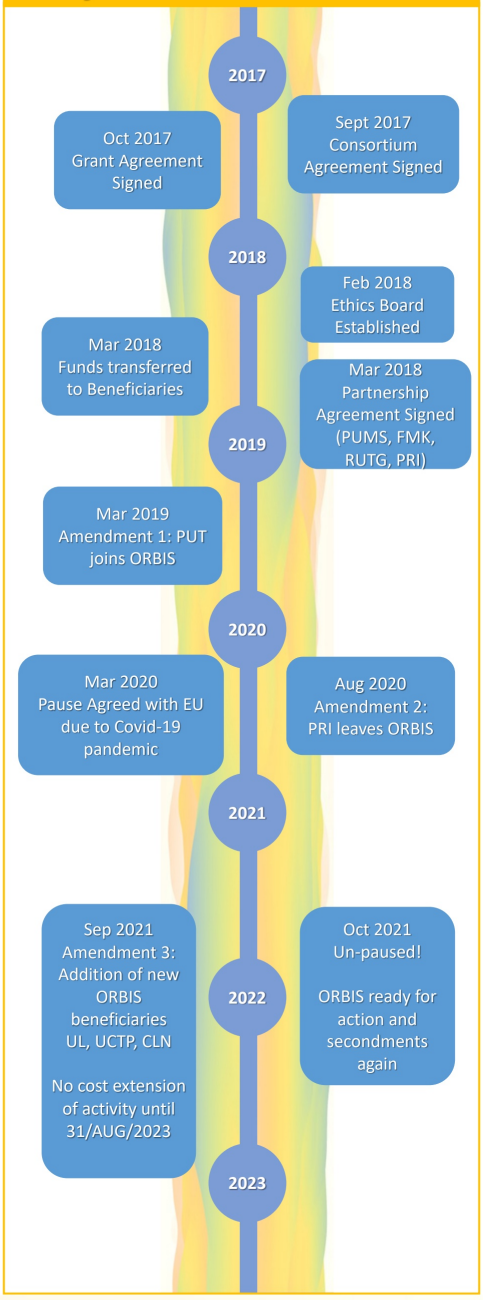
WP4	WP5	WP6	WP7
Training	Management	Communication & Dissemination	Ethics
Director Katarzyna Kosicka-Noworzyń, PUMS **Co-Director** Emilia Jakubowska, PUMS	**Lead** Janina Lulek, PUMS (PC) **Co-Lead** Bożena Raducha, PUMS	**Lead** Wojciech Smulek, PUT	**Lead** Michał Romański, PUMS
Co-Lead All 13 Consortium Members		**Co-Lead** All 13 consortium members	**Ethics Advisory Board** Poznań University of Life Sciences Polish Academy of Sciences Weill Cornell Medicine

The Project Coordinator, PC (Prof Janina Lulek, PUMS) manages the delivery of the overall programme goals and is primary contact point for the EU Research Executive Agency (REA). **The Manager** (Bożena Raducha, PUMS) supports the PC in financial and EU document administration.



The General Assembly comprises representatives from all 13 Consortium members and is the ultimate decision-making body of ORBIS, in line with the Consortium Agreement procedures.
The WP 5 Management team is supported by two bodies- **the ORBIS Training** and **ORBIS Steering Committees**, also comprised of representatives from all 13 Consortium members.

Key EU-ORBIS Timeline



Prepared by: Sharon Davin and Janina Lulek

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Essential ingredients

From WP1 to WP7

ORBIS FINAL CONFERENCE
POZNAŃ, JULY 5-6TH 2023

ORBIS focuses on development of new and more effective manufacturing and characterisation approaches leading to considerable **improvement of the biopharmaceutical properties** of drug substances, dosage forms and drug delivery systems.

WP1
Drug substances and pharmaceutical preformulation

Prof. Lidia Tajber
Trinity College Dublin

Synthesis & preformulation

Prof. Stanko Srčič
University of Ljubljana

DEVELOPMENT OF ACTIVE PHARMACEUTICAL INGREDIENTS (APIs)

comprehensive and systematic approach to pharmaceutical development
synthetic processes
Design of experiments (DOE)
Quality by design (QbD)

intrinsic, solid state and derived properties of the APIs
spectrometry and imaging techniques
thermal analysis thermogravimetry
differential scanning calorimetry (DSC)
powder X-ray diffraction (PXRD)

Figure 2: Images of nanosized needle crystals, prediction made as a new class (nidditic) and as a part of benzoic acid crystals (right)

From the work presented during 4th ORBIS Summer School:
Design of particle size and morphology
Martin Balouch[1]; Akeem Olaleye[2]; Georgia Gunning[2], Melba Simon[2], Sharon Davin[2], František Štěpánek[1]
1 Department of Chemical Engineering, University of Chemistry and Technology, Technická 3, 166 28 Prague 6,Prague, Czech Republic
2 APC Ltd, Building 11 Cherrywood Business Park, Loughlinstown, Dublin 18, Ireland

WP2
Dosage forms and drug delivery systems

Dr. Aleksandra Dumicic Zentiva

Novel drug carriers, dosage forms & drug delivery systems

Prof. Anne Juppo
University of Helsinki

ORAL DRUG DELIVERY SYSTEMS
structure of the dosage forms and drug delivery systems, such as minitablets, nano- and microparticles
coherent anti-Stokes Raman scattering (CARS), sum frequency generation (SFG), two photon electronic fluorescence (TPEF)

TOPICAL AND TRANSDERMAL DRUG DELIVERY SYSTEMS
hydrogels, organogels, creams, microemulsions, ionic liquids, unimolecular polymeric micellar formulations

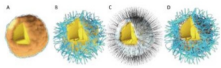


Figure 4. Illustration of curcumin nanocrystals' stabilization types. A: electrostatic (SDS), B: steric/polymeric (P188), C: phospholipids + peg-ylated pl. (DPPC+ PEG-DMPE), D: combination of steric and electrostatic (HPMC+ DPPG).

From the work presented during 4th ORBIS Summer School:
Application of nanoparticles and nanocrystals in design of advanced drug delivery systems
Denisa Lizoňová[1]; Ondřej Norvál[1,2]; Karolína Slonková[1]; Filip Hládek[1,2]; Stanislav Chvíla[1,2]; František Štěpánek[1]
[1]Laboratory of Chemical Robotics, Department of Chemical Engineering, University of Chemistry and Technology Prague,Technicka 3, 16628 Prague, Czech Republic;
[2]Zentiva k.s.,Ukatelovny130,10237 Prague, Czech Republic

WP3
Biopharmaceutical evaluation of dosage forms and drug delivery systems

Prof. Marta Karaźniewicz-Łada
PUMS

Tests of oral dosage forms in biorelevant *in vitro* conditions and *in vivo* models

Dr. Grzegorz Garbacz
Physiolution

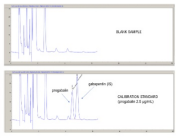
BIORELEVANT DISSOLUTION TEST METHODS
simulation the mechanical and physicochemical conditions during the gastro-intestinal passage

INVESTIGATION OF DRUG PERMEABILITY PATHWAYS
human skin co-cultures of fibroblasts and keratinocytes & novel polymers as dermal matrices

Investigation with confocal microscopy as well as scanning electron microscopy (SEM), transmission electron microscopy (TEM), Raman spectroscopy and FTIR.

Development of novel bioanalytical methods

Dr Grzegorz Garbacz demonstrates a novel dissolution test device



Lower plasma volume → Shorter analysis time → Improved sensitivity

From the work presented during 1st ORBIS Summer School:
HPLC-FLD method for the determination of pregabalin in human plasma
Katarzyna Kosicka[1], Leonid Kagan[2]
[1]Department of Physical Pharmacy and Pharmacokinetics, PUMS, Poznań, Poland
[2]Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers, the State University of New Jersey

WP4
Training

Katarzyna Kosicka-Noworzyń, PhD, DSc
PUMS

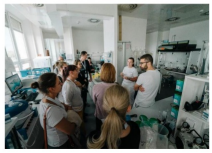
Career development of academics and industrial employees: enhancing skills and expertise

Emilia Jakubowska, PhD
PUMS

Early stage reaserchers (ESRs) support – the development of new collaborative links with high-profile academic staff abroad and valuable skills from the industry at all levels. ERCs can develop project specific skills and enhance their knowledge in the chosen research area

WP4 focused on two main activities:

1. **Secondments** training span thematically across WP1-WP3.
2. Teaching and learning activities of ORBIS included:
   - **Four Summer Schools**, for all participants
   - **Annual workshops** - to support collaboration within the project and discuss outcomes of secondments, collaborative research, and future steps.



WP5
Management

Prof. Janina Lulek
PUMS

Managing of the ORBIS project

Bożena Raducha
PUMS

ORBIS is directed by **Coordinator (CS)** supported by **Administration Staff (AS)**.

General Assembly (GA): the ultimate decision-making body of the Consortium.
Steering Committee (SC): monitoring and advice body; responsible for completing of all WP1-WP7 tasks.
Training Committee (TC): monitoring of all aspects related to secondments, training, knowledge transfer & reporting

WP6
Communication and dissemination

Wojciech Smułek, PhD
PUT

Managing of all aspects of communication

Communicating to multiple audiences about the aims and measures to be taken by the participating organisations to complete the program of the project.

Important and break-through research results for peer scientists will be prepared directly by all ORBIS participants. WP6 translates the research results into a popular style, and **delivering the news for media and other researchers**.

WP7
Ethics

To ensure compliance with the 'ethics requirements'

Michał Romański, PhD, DsC, PUMS

WP7: ensures the **compliance with ethics requirements**: human rights & protection of human beings, animal protection & welfare, data protection & privacy, environmental protection, malevolent use of research results, compliance with international, EU & national law.

Ethics Advisor Board: oversees the ongoing activities of the project, **offers advice on ethics issues** and ensure continuing compliance with the ethics standards and guidelines set in Grant Agreement.

Prepared by Dorota Danielak, Katarzyna Filip, Piotr Rudzki

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