



# DRUG DELIVERY THROUGH THE PHYSIOLOGICAL BARRIERS

International Symposium  
**24-26 April, 2025**  
Budapest, Hungary



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## Dear Colleagues, Guests, and Delegates,

It is a great pleasure and honor that we can welcome you to the „Drug Delivery through the Physiological Barriers Symposium”, 24th-26th April 2025, in the beautiful capital city of Hungary, in Budapest.

Over the course of this event, we will overview some critical aspects of drug delivery, and the various types and modeling of the biological barriers to overcome, for appropriate drug administration. Our program is designed to inspire, inform, and stimulate the discussions, networking and knowledge exchange. We are privileged to host excellent keynote speakers, invited speakers and poster presenters at different levels of scientific carrier. In today's rapidly evolving medical and pharmaceutical world, it is essential to stay up to date with trends and novel technologies. We will explore significant advancements in this field with an interdisciplinary approach including new results and innovations in pharmaceutical technology, pharmacology, biology, bioengineering, medical biotechnology, bionics, in silico modeling etc.

Our objectives for this symposium are to:

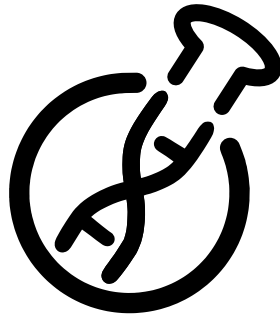
- Explore cutting-edge research in drug delivery field.
- Discuss innovative strategies
- Facilitate networking and collaboration.
- Integrate younger researchers into the scientific community
- Provide insights on leveraging trends and technologies for better medical products.

We encourage you to engage actively in the sessions, share your insights, and network with your peers. Thank you for being a part of this significant event. Let us embark on this journey of discovery and advancement together.

Sincerely yours,

**Prof. Franciska Erdő**

chair of the Symposium



**DRUG DELIVERY  
THROUGH  
THE PHYSIOLOGICAL  
BARRIERS**

**24 APRIL 2025**



# MARIA A. DELI, M.D., PH.D. DSC.

Member of the Hungarian Academy of Sciences and Academia Europaea



**Affiliation:** HUN-REN Biological Research Centre,  
Institute of Biophysics, Temesvari krt 62,  
H-6726 Szeged, Hungary

**E-mail:** [deli.maria@brc.hu](mailto:deli.maria@brc.hu)

<https://www.brc.hu/en/research/institute-of-biophysics>

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## SHORT BIOGRAPHY

Prof. Deli is the director of the Institute of Biophysics and head of the Biological Barriers Research Group at HUN-REN BRC, and honorary professor at the University of Szeged. She has been actively working in the field of biological barriers for over 30 years. She pioneered novel complex culture models for the blood-brain barrier and different epithelial barriers to investigate cellular interactions in physiological and pathological conditions and to test protective molecules as well as drug and nanoparticle permeability. Her research interests include culture models of the blood-brain, respiratory, intestinal and cornea barriers; barrier models in microfluidic devices; organ-on-chip models; protection of biological barriers; effect of natural products on biological barriers; targeted nanoparticles for drug delivery across biological barriers; cell interactions with new nanomaterials; cellular glycocalyx in barrier function; biomechanics and biophysical properties of barrier cells. Supervised 12 BSc, 17 MSc and 12 PhD dissertations. Principal investigator/consortium partner in 25 national and international grants. Scientific publications: 206, patents: 4, citations: > 13000, H-index: 55.

# ORGAN-ON-CHIP MODELS OF BIOLOGICAL BARRIERS

**Mária Deli**

*HUN-REN Biological Research Centre, Szeged, Hungary*

To bridge the translational gap between animal models and clinical therapy organ-on-chip technology offers new microphysiological systems based on human stem cells. Microfluidic chip based models have been developed and characterized for many human organs as well as for the most important barriers of the human body, the blood-brain, the respiratory, the intestinal and the skin barriers. Our research group has pioneered a versatile microfluidic lab-on-a-chip device to model the intestinal, respiratory and blood-brain barriers with the use of human cell lines and rat primary cells (Walter et al, 2016). I will present the most important types of chip devices for barrier modelling with focus on the number of channels, compartment separation by membranes or scaffolds, the use of hydrogels. Examples will be shown for the biomedical application of these chip devices, including transport and targeted delivery of drugs, modeling of diseases, investigation of toxicity and new therapeutic molecules. Since human patient-specific organoids are now included in ongoing clinical studies (Verstegen et al, 2025), organ-on-chip models will play an increasingly important role not only in preclinical but in clinical research, too.

**References:** Walter FR et al. 2016. *Sens Actuators B Chem.* 222:1209-1219.  
Verstegen MMA et al. 2025. *Nat Med.* 31(2):409-421.

# NOVEL ORGAN-ON-A-CHIP DEVICE FOR HIGH THROUGHPUT DRUG CANDIDATE SCREENING

Sepsik Norman<sup>1</sup> , Ferenc Ender Dr.<sup>1,2</sup>, György Tibor Balogh Dr.<sup>3</sup>

<sup>1</sup>*Department of Electron Devices, Faculty of Electrical Engineering and Informatics,  
Budapest University of Technology and Economics, Műegyetem rkp. 3. H-1111, Budapest, Hungary*

<sup>2</sup>*Spinsplit LLC., 2220 Vecsés, Szőlőskert utca 0182/135*

<sup>3</sup>*Department of Chemical and Environmental Process Engineering Faculty of Chemical Technology  
and Biotechnology, Budapest University of Technology and Economics, Műegyetem rkp. 3.  
H-1111, Budapest, Hungary*

**Introduction:** Organ-on-a-Chip microreactors are in vitro microfluidic devices capable of modeling the function of individual organs of a living organism. The presented Liver-on-a-chip device aims to model certain aspects of liver metabolism. In the practice of (industrial) pharmaceutical research, a biological model based on liver microsomes (endoplasmic reticulum of hepatocytes) containing the cytochrome CyP450 enzyme is used, but this system has many known limitations. The proposed model addresses known throughput bottlenecks of currently used CyP450 models by reducing the number of required reagents and by introducing continuous flow process using microreactors. A new nanocomposite system is being developed together with a microfluidic device that serves as a biomimetic alternative of the currently used in vitro biological models.

**Method:** A nanofibrous composite system was made via electrospinning (Spincube, Spinsplit LLC, Budapest Hungary) that comprised of polylactic acid (PLA) nanofibers, and metalloporphyrin (FeT-PPS) that was immobilized onto the surface of magnetic nanoparticles (MNPs) This nanocomposite was integrated into a biocompatible custom-made 3D printed microfluidic device. A demonstration measurement was carried out with the novel microreactor device to evaluate its effectiveness.

**Results:** The nanocomposite system was successfully recreated based on the previous work of the research group. The biocompatibility of the available polymeric materials was also evaluated and from PLA a 3D printed microfluidic chip was made. With this device a successful demonstration measurement was carried out, after 40 minutes about 50% conversion was measured in the conversion of amlodipine into its human metabolite dehydroamlodipine.

**Conclusions:** The previously developed nanofiber composite system was integrated into a microreactor designed for this purpose. The biomimetic operation of the microreactor was demonstrated and a significant conversion rate was achieved in the biomimetic oxidation of amlodipine to dehydroamlodipine. The current microreactor cassette could be a good candidate for further upscaling and demonstration for high throughput drug candidate screening.

**References:** B. Decsi et al., "Liver-on-a-chip-magnetic nanoparticle bound synthetic metalloporphyrin- catalyzed biomimetic oxidation of a drug in a magnechip reactor," *Micromachines* (Basel), vol. 10, no. 10, Oct. 2019, doi: 10.3390/mi10100668.

D. Balogh-Weiser et al., "Magnetic nanoparticles with dual surface functions—efficient carriers for metalloporphyrin-catalyzed drug metabolite synthesis in batch and continuous-flow reactors," *Nanomaterials*, vol. 10, no. 12, pp. 1–16, Dec. 2020, doi: 10.3390/nano10122329.

D. Balogh-Weiser et al., "Novel biomimetic nanocomposite for investigation of drug metabolism," *J Mol Liq*, vol. 368, p. 120781, Dec. 2022, doi: 10.1016/J.MOL-LIQ.2022.120781.

# THE ROLE OF LAB-ON-A-CHIP BARRIER MODELS AND BRAIN ORGANOIDs IN DRUG TESTING ACROSS THE BLOOD-BRAIN BARRIER

Fruzsina Walter, Judit P. Vigh, Anna Kocsis, Nóra Kucsápszky and Mária Deli

*HUN-REN Biological Research Centre, Szeged, Hungary*

The use of in vitro cell culture models is essential in drug development to study the penetration of potential drug compounds across biological barriers. A recent trend in drug testing research is the use of cell cultures derived from human-induced pluripotent stem cells (iPSCs) and the creation of human brain spheroids and organoids from these cells. Brain organoids are able to replicate key aspects of brain architecture and function, making them invaluable for studying toxicity and effects of drug candidates, for modeling neurodevelopmental and neurodegenerative disorders. Lab-on-a-chip systems can mimic the microfluidic environment of brain vessels, allowing more accurate analysis of drug transport across the blood-brain barrier. In our laboratory with the use of brain organoids we were able to test the entry of guest molecules carried by nanoparticles to the tissue (Veszeka et al, 2021; Mészáros et al, 2023). Previously we have developed a versatile microfluidic lab-on-a-chip device to model biological barriers (Walter et al, 2016). Now we have advanced this microelectronic biochip by combining a human stem cell-based dynamic blood-brain barrier model with iPSC-derived brain organoids. With this we have built a unique platform to study the penetration of molecules across the blood-brain barrier together with tracking the entry of the agents into brain organoids. We are convinced that lab-on-a-chip systems, brain organoids and their combination are revolutionizing neuroscience and drug development by providing more accurate, human-relevant testing platforms and they also pave the way to personalized medicine.

**References:** Walter FR et al. 2016. *Sensors and Actuators B: Chemical*. 222(1209-1219).  
Veszeka S et al. 2021. *Pharmaceutics*. 14(1):86.  
Mészáros M et al. 2023. *Cells*. 12(3):503.

**Funding:** The project was supported by the National Research, Development and Innovation Office (NKFIH), NNE-129617 & OTKA-K 143766 (to M.A.D.), OTKA-PD 138930 (to M.M.), the Secretariat of the Hungarian Research Network (former ELKH, SA-111/2021 to F.R.W.), and by the University Research Scholarship Programme (EKÖP-24-2-SZTE-449 to A.E.K.), which is a scholarship of the Ministry of Culture and Innovation funded by the NKFIH.

# DRUG DELIVERY THROUGH THE BIOLOGICAL BARRIERS STUDIES AT PÁZMÁNY PÉTER CATHOLIC UNIVERSITY

**Franciska Erdő, Dorottya Kocsis, Mária Laki, András Laki, Tamás Garay and  
Gábor Szederkényi**

*Pázmány Péter Catholic University, Faculty of Information Technology and Bionics,  
Práter u. 50/a, 1083 Budapest, Hungary*

**Introduction:** In the last decade, pharmaceutical research has increasingly focused on new, innovative dosage forms and drug delivery systems. These novel formulations can greatly enhance the absorption, bioavailability and clearance kinetics of active ingredients. Modern drug delivery techniques are being investigated for a wide variety of dosing routes (e.g. topical, nasal, ophthalmic, central, systemic etc.). At the Faculty of Information Technology and Bionics of PPCU, we have also been involved in this research, primarily in connection with the examination of the blood-brain barrier, the nasal barrier, the skin and the eye under physiological and pathological conditions.

**Methods:** Our methodological toolbox includes fabrication and validation of microfluidic testing platforms, microscopic and imaging techniques, in vitro and ex vivo diffusion studies, in vivo rodent and human investigations, 3D bio-printing and 3D printing, tissue engineering, mathematical simulation and prediction.

**Results:** In case of blood-brain barrier, we successfully demonstrated the transient opening of the barrier with transporter inhibitors, while with nasal dosing, we were able to increase brain exposure by parallel local vasoconstriction and transporter inhibition. In the skin, we analyzed the chemical composition, permeability and change in barrier function and tissue integrity of various human and animal skin samples and also in artificial skins after mechanical, chemical and physical insults. We set up an in vivo wound healing model, in which we test active ingredient-containing wound dressings, and in our eye-on-a-chip system, we can also evaluate ophthalmic preparations.

**Conclusions:** In summary, over the past few years, we have established an assay system at our Faculty that is suitable for comparing and optimizing different drug formulations and with which, we can characterize various in vitro cellular systems, ex vivo tissues, artificial tissues and in vivo organisms in physiological and pathological conditions.

## References:

1. Lunter D et al, Progress in Topical and Transdermal Drug Delivery Research-Focus on Nanoformulations. *Pharmaceutics*. 2024 Jun 16;16(6):817
2. Szederkényi G et al, Mathematical modeling of transdermal delivery of topical drug formulations in a dynamic microfluidic diffusion chamber in health and disease. *PLoS One*. 2024 Apr 11;19(4):e0299501
3. Ponmozhi J et al, Models for barrier understanding in health and disease in lab-on-a-chips. *Tissue Barriers*. 2024 Apr 2;12(2):2221632. doi: 10.1080/21688370.2023.2221632

# DRUG DELIVERY THROUGH THE PSORIATIC EPIDERMAL BARRIER

Dorottya Kocsis<sup>1</sup>, Szabina Horváth<sup>2</sup>, Fabiola Kreis<sup>3</sup>, Kende Lőrincz<sup>3</sup>,  
Roland Csépanyi-Kömi<sup>3</sup>, and Franciska Erdő<sup>1</sup>

<sup>1</sup>Pázmány Péter Catholic University, Budapest, Hungary, <sup>2</sup>University of Pécs, Pécs, Hungary  
<sup>3</sup>Semmelweis University, Budapest, Hungary

**Introduction:** Psoriasis is a chronic immune-mediated skin disease with a complex pathological background. It is characterized by scaly, erythematous plaques that mainly affect the elbows, knees, scalp and nails. The prevalence ranges from 1% to 3% in the general population, affecting more than 125 million people worldwide. Therapeutic options for psoriasis include topical therapies, phototherapy, and systemic treatments. Initial treatments focus on topical agents such as vitamin D analogues or corticosteroids, often used in combination or with occlusion to enhance efficacy. When topical treatments are insufficient, second-line options are needed, such as phototherapy and systemic therapies such as methotrexate, cyclosporine, and acitretin. Despite the wide use of topical drugs, little data are available on changes in psoriatic skin permeability, so the main objective of this study was to investigate drug penetration at various stages of the disease using an imiquimod-induced wild type mouse model.

Transient Receptor Potential Vanilloid 1 (TRPV1) and Ankyrin 1 (TRPA1) are nonselective cation channels activated by various ligands, temperature, or pH changes. While TRPV1 seems to be essential for the development of chronic inflammatory diseases such as psoriasiform dermatitis, and its blocking leads to severely impaired inflammation, TRPA1 exerts a protective role, and blocking TRPA1 enhances the inflammatory symptoms. The exact mechanism and its effect on skin permeability have not been previously investigated in TRPV1 and TRPA1 knockout mice. Consequently, the second aim of our study was to address this knowledge gap.

**Method:** The psoriasis model was validated using different methods, including measurements of body and spleen weight, skin thickness and blood perfusion. We used an inflammatory cytokine ELISA array and Raman spectroscopy for chemical-molecular characterization. Scanning electron microscopy, two-photon microscopy and ultrasound imaging were performed for morphological analysis, while transepidermal water loss was measured as a validation of barrier function before drug permeability studies.

**Results:** The mice exhibited the hallmark symptoms, including thick, red patches of skin with silvery white scales. Significant weight loss and splenomegaly were observed, caused by systemic inflammation. Furthermore, the levels of various molecules associated with regulating barrier function and immune response, including ceramides, cholesterol, and proteins (particularly inflammatory cytokines), were found to be elevated in the diseased groups. The psoriatic group showed increased permeability during disease progression. In wild type and TRPA1 KO mice, enhanced skin thickness and hyperkeratosis blocked further increase of drug penetration at the late phase. Although paracellular connections (tight junctions) become loose in the advanced phase, hyperkeratosis blocked drug delivery through the transappendageal routes.

**Conclusions:** Our results indicate that topical drug therapy can be more effective in early phases of plaque development.

**References:** Kocsis D et al. 2022. *Int. J. Mol. Sci.* 23(8), 4237.  
Asbóth D et al. 2024. *Ital J Dermatol Venerol.* 159(3):303-317.

# COMPARTMENTAL MODELING AND PARAMETER ESTIMATION OF TRANSDERMAL DELIVERY OF TOPICAL DRUG FORMULATIONS

Gábor Szederkényi, and Franciska Erdő

*Pázmány Péter Catholic University, Faculty of Information Technology and Bionics,  
Práter u. 50/a, 1083 Budapest, Hungary*

**Introduction:** Studying and mathematically modeling the transdermal delivery of drugs is crucial for optimizing drug absorption through the skin, ensuring effective therapeutic outcomes while reducing side effects. Mathematical models help predict how different factors, such as drug properties, skin permeability, and delivery system design, influence drug transport. These models can efficiently support the development of transdermal drug delivery systems, improving their efficiency and patient compliance. Additionally, such studies can reduce the need for extensive animal testing and streamline the design of new, more effective drug formulations.

**Method:** The skin penetration of topically administered caffeine cream was investigated in a skin-on-a-chip microfluidic diffusion chamber at room temperature and at 32 degrees Celsius. Also the transdermal penetration of caffeine in healthy and diseased conditions was compared in mouse skins from intact, psoriatic and allergic animals. In the last experimental setup dexamethasone, indomethacin, piroxicam and diclofenac were examined as a cream formulation for absorption across the dermal barrier. The partial differential equation describing transdermal delivery of topical drugs was spatially discretized. The key dynamical properties of the resulting compartmental ordinary differential equation were analyzed.

**Results:** It was proved that the applied mathematical model was structurally identifiable which gives the possibility to uniquely determine the model parameters from available measurements. The model parameters were estimated using numerical optimization. The model computed and measured results showed a good match in every studied case.

**Conclusions:** Our results indicate that the proposed mathematical model might be applied for prediction of drug delivery through the skin under different circumstances and for various drugs in the novel, miniaturized diffusion chamber. The utilization or further extension of our model greatly depends on the therapeutic goal and the properties of the applied topical products.

## References:

- [1] Anissimov, Y. G., Jepps, O. G., Dancik, Y., & Roberts, M. S. (2013). Mathematical and pharmacokinetic modelling of epidermal and dermal transport processes. *Advanced drug delivery reviews*, 65(2), 169-190.
- [2] Szederkényi, G., Kocsis, D., Vághy, M. A., Czárán, D., Sasvári, P., Lengyel, M., ... & Erdő, F. (2024). Mathematical modeling of transdermal delivery of topical drug formulations in a dynamic microfluidic diffusion chamber in health and disease. *Plos one*, 19(4), e0299501.

# TARGETED SKIN BARRIER REPAIR: ENHANCING BARRIER FUNCTION THROUGH VESICLE-ENCAPSULATED CERAMIDE DELIVERY

Kende Lőrincz

*Semmelweis University, Department of Dermatology, Venerology and Dermatatooncology 1085  
Budapest Mária str. 41.*

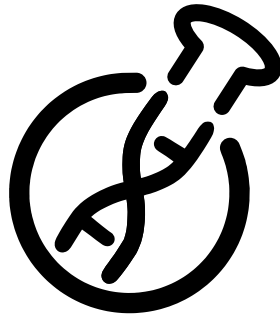
**Introduction:** Atopic dermatitis (AD) and other chronic skin conditions characterized by dryness and barrier dysfunction, such as xerosis and ichthyosis, are highly prevalent across Europe. Studies report that AD affects approximately 15-20% of children and 1-3% of adults in many European countries, contributing to a significant disease burden. Clinical guidelines emphasize that effective skin barrier management, particularly through the use of moisturizers, is essential not only for AD but also for other dryness-associated skin disorders. Selecting appropriate and effective moisturizers plays a critical role in preventing exacerbations, maintaining remission, and improving patients' quality of life.

**Materials and Methods:** This summary presentation focuses on the role of ceramides and vesicular delivery systems, particularly multivesicular emulsion (MVE) technology, in strengthening the skin barrier. By exploring the efficacy of ceramide-based formulations, the aim is to provide insights into optimizing treatment strategies for AD through innovative drug delivery methods.

**Results:** Ceramides are vital components for maintaining skin permeability barrier integrity and hydration. They also regulate immune responses by modulating anti-inflammatory and antimicrobial defenses. AD patients often exhibit reduced ceramide levels, structural abnormalities, and increased transepidermal water loss, leading to a compromised skin barrier. Clinical studies demonstrate that ceramide-enriched moisturizers are both safe and effective in reducing symptoms for both children and adults with AD. MVE technology enables a controlled and sustained release of ceramides into the stratum corneum (SC), facilitating barrier repair and enhancing patient adherence to treatment regimens.

**Conclusion:** Recommending clinically validated ceramide-dominant moisturizers with optimized ingredient levels, ratios, and structures, alongside effective vesicular delivery technologies, can significantly improve disease control and prevent flare-ups in AD. This approach not only alleviates symptoms but also reduces the overall burden of AD on patients, families, and healthcare systems.





# **DRUG DELIVERY THROUGH THE PHYSIOLOGICAL BARRIERS**

**25 APRIL 2025**



# WINFRIED NEUHAUS

**AIT Austrian Institute of Technology GmbH & Danube Private University  
(DPU) Krems**



## SHORT BIOGRAPHY

**Winfried Neuhaus** is one out of six Principal Scientists at the AIT and heading the group Biological Barriers. He studied food- and biotechnology at the University of Natural Resources and Life Sciences in Vienna Austria and received his PhD from the University of Vienna Pharmaceutical Sciences. Before he joined the AIT, he worked at the University Hospital Wurzburg Germany as PI for six years and was granted his habilitation in Molecular Medicine. In addition, he was employed at the Medical University Vienna Institute of Medical Genetics, 2015-2016 and the University of Vienna Department of Pharmaceutical Chemistry, 2013-2016. Before he started in Wurzburg in 2010,

he was leader of the "Preclinical and Blood-Brain Barrier Research Group" in the pharmaceutical industry company PharmaCon GmbH for two years. In total, Winfried Neuhaus has over 20 years expertise in the biological barriers research field especially for in vitro models and in vitro/in vivo translatability in health and disease. He has supervised over 25 master theses and 10 doctoral theses. He is author of >75 publications in peer-reviewed journals, most of them with first or corresponding authorships, five book chapters, one book and > 100 abstracts. He is engaged as reviewer for several scientific journals and funding agencies, member of several advisory boards, member of the EPAA mirror group, the current president of the European Society for Alternatives to Animal Testing EUSAAT, coordinator of the 3Rs centre network EU3Rnet and Professor for 3Rs and New Approach Methodologies at DPU Krems, Austria.

# REFLECTIONS AND STORIES ABOUT THE WORK WITH BLOOD-BRAIN BARRIER IN VITRO MODELS

Winfried Neuhaus,<sup>1,2</sup>

<sup>1</sup>*Competence Unit Molecular Diagnostics, AIT - Austrian Institute of Technology GmbH,  
1210 Vienna, Austria*

<sup>2</sup>*Faculty of Medicine and Dentistry, Danube Private University (DPU) Krems,  
3500 Krems, Austria*

The lecture will take a closer look at in vitro models of the blood-brain barrier (BBB) as an example of biological barriers. In particular, the extent to which in vitro models can or must simulate the physiology of the human BBB will be discussed on the basis of application examples.

This includes the necessity of a paracellular barrier, how this can be achieved and influenced, which cell types are necessary, what influence do the cell sources have and are species differences relevant in the models.

The topics of reproducibility and comparability of studies, the role as a model for the replacement of animal experiments and above all how complex a model must be are dealt with.

In summary, experiences will be shared and questions raised and discussed based on data and examples, which should emphasize that in vitro models of biological barriers need to be validated and adapted for each individual question.

# CROSSING OF THE PATHOGENS AND DRUGS ACROSS THE BLOOD BRAIN BARRIER: FEW SIMILARITIES, MORE DISPARITIES

Mangesh Bhide<sup>1,2</sup>

<sup>1</sup>*Laboratory of Biomedical Microbiology and Immunology, University of Veterinary Medicine and Pharmacy in Kosice, Komenského 73, 041 81 Košice, Slovakia*

<sup>2</sup>*Institute of Neuroimmunology, Slovak Academy of Sciences, Dúbravská cesta 9, 845 10 Bratislava, Slovakia*

**Introduction:** Organisms that have crossed the species barrier from animals to humans include several pathogens like viruses (such as Hendra, Nipah, SARS, and influenza), as well as bacteria (*Borrelia*, *Streptococcus*, etc.) and others. It is still unclear why new pathogens like SARS-CoV-2, which appears to cause respiratory symptoms, manage to cross the blood-brain barrier (BBB) and enter the brain. And what exact mechanisms do they use to get over the BBB, after all? Since infectious diseases of the central nervous system (CNS) are very hard to treat, they generally continue to be a significant cause of morbidity and mortality. A major obstacle for curing brain diseases is the blood-brain barrier (BBB), which impedes therapeutic agents to reach the brain and target the pathogens.

**Method:** The second part of the talk will provide an overview of our efforts in developing a proof-of-concept drug delivery nanosystem coated with CDR3-peptides or pathogen-specific nanobodies (Nbs) to target brain infections.

**Results:** The nanosystem is equipped with BBB-homing moiety, which can enhance its translocation across BBB via the receptor-mediated transcytosis. The nanosystem is loaded with antiviral or antibacterial agents to allow specific release of drug-payload in CNS. Finally, some exciting results will be presented to demonstrate how nanosystems are non-toxic to cells, how they effectively kill antibiotic-resistant bacteria, how they kill pathogens in less time than traditional antibiotics, how they achieve better biodistribution in the CNS, and how they save animals with CNS infections more effectively than traditional drugs.

**Conclusions:** We anticipate attracting an audience in the fascinating field of developing nanosystems for drug delivery to the CNS: the nanosystem which is designed around fundamental principles of host-pathogen crosstalk. Research supported by EURONANOMED2021-105 (Antineuropatho), APVV-22-0084, APVV-18-0259 VEGA 1/0348/22 and 1/0381/23.

# IN VITRO RECONSTRUCTED 3D MODELS OF HUMAN DUODENUM, JEJUNUM AND ILEUM

**Marek Puskar<sup>1</sup>, Jan Markus<sup>1</sup>, Zachary Stevens<sup>2</sup>, Jonathan Cheong<sup>3</sup>, Mitchell Klausner<sup>2</sup>, Alex Armento<sup>2</sup>, Seyoum Ayehunie<sup>2</sup>**

<sup>1</sup>*MatTek In Vitro Life Science Laboratories, Bratislava, Slovakia*

<sup>2</sup>*MatTek Corporation, Ashland, MA, United States of America*

<sup>3</sup>*Genentech, San Francisco, CA, United States of America*

The study of gastrointestinal (GI) toxicity is limited due to the lack of physiologically relevant in vitro models that recapitulate the role of specific parts of the GI tract. For example, traditional in vitro cell cultures approach utilizes immortalized human Caco-2 cell line cultured for about 21 days to mimic properties of small intestine mucosa and assess ADME properties of drugs. However, these models are limited by the fact that they originate from cancer cells, have unphysiological expression and/or functionality of major drug transporters and drug metabolizing enzymes, do not have fully polarized structural features, and are not predictive of GI toxicity even though they have been in use for more than 5 decades. To mimic the physiology and functionality of the human gut, we established the small intestinal model from primary human cells, which recapitulates many aspects of small intestine biology. The only pitfall of this model is that it only consists of cells derived from jejunum.

Here we present development of 3 new models of small intestine utilizing primary cells from different intestine regions in order to provide further physiological relevance and expand ability to pinpoint differences between different regions of small intestine mucosa (duodenum, jejunum, and ileum).

The newly developed 3D tissues mimic morphology of normal intestinal epithelium with structural features resembling villi and physiological-like barrier function. Gene expression analyses revealed differences in the expression of genes encoding transporter proteins (ABC family, peptide transporters) and drug metabolizing enzymes in various regions. On the other hand, expressions of some drug metabolizing enzymes such as CYP3A4, CYP2C9, UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1), and Carboxylesterase 1 (CES-1) were maintained in each segment at a comparative level. Our preliminary experiments aimed at drug absorption and metabolism revealed that the permeation of Vinblastine was affected by inhibition of MRP and/or P-gP transporters. The activity of metabolic enzymes (phase II glucuronidase enzymes) was suggested by the presence of raloxifene-6-glucuronide metabolite following the treatment of tissues with raloxifene, which was sensitive to inhibition with glucuronidase inhibitor.

These results suggest that the reconstructed tissues from the three segments of the small intestine may serve as useful tools to predict both investigational and traditional GI drug safety and absorption in the GI tract. In addition, use of these models will reduce animal use and improve the pre-clinical drug development process.

# ENHANCING BIOAVAILABILITY OF A NON-STEROIDAL ANTI-INFLAMMATORY DRUG THROUGH PULMONARY DELIVERY

Heba Banat, Rita Ambrus and Ildikó Csóka

*Institute of Pharmaceutical Technology and Regulatory Affairs, Faculty of Pharmacy,  
University of Szeged, Eötvös u.6, H-6720 Szeged, Hungary*

**Introduction:** Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic, anti-inflammatory, and antipyretic effects. However, their use is often associated with gastrointestinal, cardiovascular, and renal side effects. Additionally, their poor water solubility poses challenges for oral and injectable formulations. Therefore, developing alternative delivery systems to mitigate these drawbacks is crucial. Pulmonary delivery presents a promising approach, offering enhanced absorption, high bioavailability, and a rich blood supply due to its large surface area (70–100 m<sup>2</sup>) and thin epithelial barrier (0.2–0.5 µm) (Banat et al., 2023).

**Method:** Advanced particle engineering methods were employed to ensure deep lung deposition. Nanosuspensions (NS) were initially produced via wet media milling (Banat et al., 2024), followed by nano spray drying to generate an inhalable dry powder (DPI). The powders were characterized by size, morphology, aerosol performance, and dissolution rate. Cytotoxicity and permeability studies were conducted on alveolar and bronchial cell lines. Rats were used as a model to investigate bioavailability and pharmacokinetic (PK) profiles, with a single dose of 3 mg/kg administered orally and intratracheally.

**Results:** The NS had a particle size of approximately 165 nm. After nano-spray drying, the final particle size of the powder was 2–3 µm. The formulation demonstrated enhanced aerodynamic properties and improved drug release profiles. Cell line studies confirmed its biocompatibility and potential for effective lung permeation. Oral administration of the nanosuspension led to a significant increase in bioavailability compared to the raw drug. Notably, intra-tracheal powder administration resulted in an improved PK profile compared to oral NS delivery. The presence of excipients played a critical role in the formulation, ensuring its superiority for delivering the NSAID by inhalation.

**Conclusions:** The developed DPI demonstrated its suitability for pulmonary delivery. The inclusion of such excipients significantly influenced powder performance, as evidenced by the highest C<sub>max</sub> recorded for the intra-tracheally delivered sample. Overall, a promising solution for pulmonary NSAID delivery was achieved, offering a balanced approach to safety, efficacy, and applicability.

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**Acknowledgement:** This work was supported by NKFI OTKA K\_146148 project.

# DEVELOPMENT OF PRESERVATIVE-FREE NANOFIBROUS OPHTHALMIC INSERTS FOR THE TREATMENT OF BACTERIAL CONJUNCTIVITIS

Houssam Aaref Abboud<sup>1</sup>, Eszter Farkas<sup>1</sup>, Nándor Nagy<sup>2</sup>, Romána Zelkó<sup>1</sup>,  
Adrienn Kazsoki<sup>1</sup>

<sup>1</sup> University Pharmacy Department of Pharmacy Administration, Semmelweis University, Budapest, Hungary

<sup>2</sup> Department of Anatomy, Semmelweis University, Budapest, Hungary

**Introduction:** Conventional ocular drug delivery systems, such as eye drops and gels, suffer from short residence times, low bioavailability, and the need for frequent administration. Additionally, preservatives in these formulations can cause ocular irritation and long-term toxicity. Nanofibrous ocular inserts offer a preservative-free, solid-state alternative, providing prolonged drug retention and sustained release. This study aims to develop electrospun polyvinyl alcohol (PVA) and poloxamer 407-based nanofibers loaded with levofloxacin (LEVO) and to investigate the effects of hydroxypropyl beta-cyclodextrin (HP- $\beta$ -CD) and sodium hyaluronate concentrations on fiber formation, drug release, antimicrobial efficacy, and biocompatibility.

**Methods:** Mowiol® 18-88 and poloxamer 407 were used to fabricate nanofibers via electrospinning. HP- $\beta$ -CD was incorporated in 1:1 and 1:1.5 molar ratios to enhance drug solubility. Morphology was assessed using scanning electron microscopy, while physicochemical properties were evaluated via Fourier-transform infrared spectroscopy (FT-IR) and X-ray diffraction. In vitro drug release studies were conducted, and irritation potential was assessed in vivo using the hen's egg test. Antimicrobial efficacy was evaluated using the disc diffusion method, minimum inhibitory concentration, and time-kill assays to determine bacterial susceptibility and bactericidal kinetics.

**Results:** Electrospinning successfully produced fibrous nanostructures regardless of PVA molecular weight or drug:CD ratio. FT-IR and X-ray diffraction confirmed the formation of an amorphous solid dispersion. All formulations exhibited rapid and complete drug release. Antimicrobial studies demonstrated that formulations with higher HP- $\beta$ -CD content exhibited enhanced or comparable antibacterial activity to commercially available eye drops. Formulations with increased sodium hyaluronate concentrations showed strong bactericidal effects. However, cytotoxicity testing indicated that the 1:1.5 drug:CD ratio induced eye irritation.

**Conclusion:** The developed preservative-free, solid-state nanofibrous ocular inserts present a promising alternative to conventional eye drops for bacterial conjunctivitis treatment. These formulations provide sustained drug release, potent antimicrobial activity, and improved bioavailability while eliminating the need for potentially harmful preservatives. Mowiol® 18-88-based nanofibers with a 1:1 LEVO:HP- $\beta$ -CD molar ratio demonstrated the best balance of efficacy and safety, highlighting their potential as a next-generation ophthalmic treatment.

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# RATIONAL DESIGN OF NASAL DRUG DELIVERY SYSTEMS

Aleksandar Széchenyi<sup>1</sup>, Fruzsina Gósi<sup>1</sup>, Szilárd Pál<sup>1</sup>

<sup>1</sup>University of Pécs, Faculty of Pharmacy, Institute for Pharmaceutical Technology and Biopharmacy, Pécs, Hungary

**Introduction:** Effective drug delivery to the central nervous system (CNS) remains a great challenge due to the shielding properties of the blood-brain barrier (BBB) [1]. Traditional methods of systemic drug delivery often struggle to reach effective concentrations of substances like dopamine in the CNS because of BBB, which restricts drug permeability. Nasal delivery offers a promising alternative by allowing drugs to bypass the BBB, thus improving CNS drug delivery [1] [2]. However, creating effective nasal delivery systems comes with its own set of challenges, such as optimizing drug absorption, overcoming mucosal barriers, and ensuring that the drug remains stable and is released in a way that targets the CNS effectively. This study focuses on overcoming these challenges through the rational design of a novel nasal delivery system.

**Methods:** This research employed a comprehensive approach, integrating physiological, biochemical, and pharmacokinetic data to design and optimize a nanoparticle-based nasal drug delivery system. Based on excessive data analysis in published research papers, analytical and kinetic models were developed to predict and verify dopamine's release and diffusion behaviors through the nasal epithelium.

**Results:** The primary outcome of this study is the creation of a conceptual model for the rational design of nasal drug delivery systems that focus on improving CNS targeting. The model suggests using sterically stabilized polylacto-co-glycolic acid nanoparticles incorporated into a hydrogel as an optimal carrier for dopamine. This design will provide a controlled release and effective transport through the nasal mucosa while reducing enzymatic degradation. While initial in vitro results are encouraging, the effectiveness and reliability of the delivery system needs to be confirmed through more studies to validate its potential for therapeutic use.

**Conclusions:** These findings underscore the potential of rational design in creating effective nasal drug delivery systems aimed at the CNS. By leveraging specific physical and chemical properties of materials along with controlled delivery kinetics, we can enhance drug bioavailability and, in turn, improve therapeutic efficacy in the CNS. The next steps involve optimizing the formulations to encapsulate a broader range of therapeutic agents.

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# NANOFIBROUS CARRIERS FOR ADVANCED ENZYME REPLACEMENT THERAPIES

## PAVLE ANDJUS

**Diána Balogh-Weiser<sup>1,2</sup>, Gergő D. Tóth<sup>2</sup>, Ferenc Ender<sup>3,4</sup>, Nikolett Kállai-Szabó<sup>5</sup>, Adrienn Nochta-Kazsoki<sup>6</sup>, Gábor Katona<sup>7</sup>, Romána Zelkó<sup>6</sup>, István Antal<sup>5</sup>, György T. Balogh<sup>8</sup>**

<sup>1</sup>*Budapest University of Technology and Economics (BME),*

*Dept. of Organic Chemistry and Technology, Műegyetem rkp.3., 1111 Budapest, Hungary*

<sup>2</sup>*BME, Dept. of Physical Chemistry and Materials Science, Műegyetem rkp.3.,  
1111 Budapest, Hungary*

<sup>3</sup>*BME, Dept. of Electron Devices, Magyar tudósok körútja 2., 1117, Budapest, Hungary*

<sup>4</sup>*Spinsplit LLC, Szőlőskert u. 0182/135, 2220, Vecsés, Hungary*

<sup>5</sup>*Semmelweis University (SE), Dept. of Pharmaceuticals, Hőgyes E. u. 7–9, 1092 Budapest, Hungary*

<sup>6</sup>*SE, University Pharmacy Dept. of Pharmacy Administration, Hőgyes E. u. 7–9,  
1092 Budapest, Hungary*

<sup>7</sup>*University of Szeged, Inst. of Pharmaceutical Technology and Regulatory Affairs, Eötvös u. 6,  
6720 Szeged, Hungary*

<sup>8</sup>*SE, Dept. of Pharmaceutical Chemistry, Hőgyes E. u. 7–9, H-1092 Budapest, Hungary*

**Introduction+:** Enzyme replacement therapies (ERT) involve the administration of specific enzymes, which are either deficient or absent in the human body, to correct existing defects or to prevent the development of complications. Non-systemic ERT means the localized delivery of an enzyme, such as oral administration to treat metabolic dysfunctions in the gastrointestinal tract. In this research, electrospinning as a novel pre-formulation technique for enzymes was investigated. Lipases as model enzyme were selected since it widely used in pancreatic ERT. Electrospinning-based nanoformulation method allows for high polymer diversity, provides gentle conditions for sensitive enzyme, and is cost-effective and scalable, making it easy to integrate into various stages of pharmaceutical development.

**Method:** Electrospinning technique was used for the solid formulation of different types of lipases. Polyvinyl alcohol (PVA), polylactic acid (PLA) and polyvinylpyrrolidone (PVP) polymers were selected as nanofibrous carrier precursor. Specific enzyme activity, stability, mechanical and rheological properties were investigated.

**Results:** In all cases, the viscosity of the enzyme-loaded electrospun precursor mixtures was found to be lower than that of the enzyme-free solution and the average fiber diameter also decreased due to the presence of enzymes. The specific enzymatic activity (UE) of lipase entrapped in nanofibers and native enzyme was determined in intestinosolvent assay to mimic the proper GI conditions. Enzymes using entrapped in nanofibers showed remarkably higher UE than native form. Nanofibrous PLA matrix was always linked with a considerably greater increase in UE than using the PVP or PVA matrices.

**Conclusions:** Based on a comparison with commercial formulations, it can be concluded that lipase formulations using electrospun nanofibers showed comparable or higher activity with commercial lipase formulas. Electrospinning-based nanoformulation method allows for high polymer diversity, provides gentle conditions for sensitive enzyme, and is cost-effective and scalable, making it easy to integrate into various stages of pharmaceutical development.

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# UTILIZATION OF VARIOUS GELLING AND MUCOADHESIVE AGENTS FOR NASAL DELIVERY OF POLYMERIC MICELLES

Bence Sipos<sup>1</sup>, Gábor Katona<sup>1</sup>, Ildikó Csóka<sup>1</sup>

<sup>1</sup>University of Szeged, Faculty of Pharmacy, Institute of Pharmaceutical Technology and Regulatory Affairs, Eötvös u. 6., 6720 Szeged, Hungary

**Introduction:** Controlled drug release and permeation through the nasal mucosa is a challenging field of pharmaceutical research & development. Especially for nanoparticles, which tend to have a rapid drug release and absorption profile, therapeutic needs may oppose to this advantage, i.e., sustained release should be achieved either locally or through the absorption routes. Various cellulose derivatives forming gel-like structures or thermoresponsive polymers forming in situ gels can be utilized to control the liberation of nanocarriers from their matrix. Our aim was to test different type of gelling and mucoadhesive agents to determine the controllability of polymeric micelles at nasal conditions.

**Method:** The effect on micelle size and size distribution was investigated at multiple points after their co-formulation with mucoadhesive or gelling agents. The drug release and passive diffusion studies were carried out at simulated nasal conditions. Kinetic modelling was utilized also to describe the drug release profile of various formulations.

**Results:** As multiple formulations were tested with various compositions, the criteria for selecting optimal formulations were based on the stability of micelle size. Respectively to the encapsulated drugs, the micelle size ranged between 80 – 150 nm in monodisperse size distribution, with a polydispersity index below 0.300. Generally, lower concentrations of mucoadhesive (hyaluronic acid, chitosan) and in situ gelling agents (i.e., Poloxamer 407) proved also to help to increase the water solubility of the incorporated drug. Higher concentrations showed that they either have no effect or they decrease the solubilization. Various drug release and absorption profiles were also obtained based on concentration and composition. Low concentrations of chitosan for example showed a Higuchi-kinetics mediated rapid drug release profile, while at higher concentrations, with the higher molecular weight chitosan applied, sustained release was achieved.

**Conclusions:** In conclusion, our results proved that the proper selection of excipients would hinder the burst-like drug release and absorption profile of polymeric micelles, turning them into sustained release nasal dosage forms, which may be useful in local treatment of upper respiratory tract diseases or to control permeation through the blood-brain barrier in psychiatric diseases.

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# POLYMERIC NANOCARRIERS FOR INTRANASAL DELIVERY OF CANNABIDIOL IN NEURODEVELOPMENTAL DISORDERS

Rania Awad<sup>1</sup>, Avi Avital<sup>2</sup>, Alejandro Sosnik<sup>1</sup>.

<sup>1</sup> *Department of Materials Science and Engineering,  
Technion-Israel Institute of Technology, Haifa, Israel.*

<sup>2</sup> *Department of Occupational Therapy, Faculty of Health Sciences,  
the University of Haifa, Haifa, Israel.*

**Introduction:** Neurodevelopmental disorders include autism spectrum disorder (ASD) affect 5.9% of the global population. Recently, research indicated the potential therapeutic use of cannabidiol (CBD) to treat different neurodevelopmental disorders, including ASD. Intranasal drug delivery (i.n.) is a non-invasive and painless administration route that enhances drug bioavailability in the brain by bypassing the blood-brain barrier. However, i.n. has limited bioavailability due to the low nasal mucosa permeability. Various polymeric nanoparticles (NPs) have been investigated for i.n. delivery with different success. In this study, we investigate the nanoencapsulation of CBD within self-assembled polymeric NPs for the nose-to-brain delivery in ASD to increase the bioavailability of the CBD in the brain.

**Methods:** The nanoencapsulation of CBD within self-assembled polymeric NPs, namely poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (PEO-PPO-PEO) polymeric micelles, was assessed. CBD-loaded system was characterized by different methods. The compatibility was assessed in the nasal septum epithelium cell line RPMI 2650. In vitro permeability studies were conducted using RPMI 2650 cell monolayers cultured in semipermeable membranes 2650. The accumulation of CBD loaded NPs labeled with near infra-red fluorescent dye in the brain measured after i.n. and oral administration after 20 and 45 min using IVIS spectrum CT imaging (IVIS-CT). Pharmacokinetic (PK) studies were conducted to assess the CBD concentration in rat plasma and brain tissues, PK parameters were measured and analyzed. Then, the effect of i.n. and oral administration of CBD-loaded NPs on a social cooperation test, which is a relevant behavioral test in ASD model in rats was investigated.

**Results:** Initially, we produced Pluronic® F127 polymeric micelles loaded 25% w/w of CBD, with size of  $23 \pm 1$  nm with suitable physical properties for i.n. administration. Then, Pluronic® F127 nanoparticles (F127 NPs) in medium showed good compatibility and permeability in RPMI 2650 cells. In the IVIC-CT study the accumulation of i.n. administration of CBD loaded F127 in the rat's brains was higher than the orally. Pharmacokinetic analysis of rat brain tissues revealed that, 20 minutes after administration, the concentration of CBD was higher following a 5 mg/kg nasal administration compared to a 15 mg/kg oral administration of CBD-loaded F127. Followed by i.n. administration of CBD loaded F127 improved the social cooperation performance of ASD model in rats as compared to oral and control groups.

**Conclusion:** In this study we successfully developed a suitable NPs for i.n. administration and investigated the potential use of CBD for the treatment of ASD through i.n. drug delivery.

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# PROF. DR. STEFAN MÜHLEBACH

University of Basel, Dept. Pharmaceutical Sciences



## SHORT BIOGRAPHY

**Stefan Mühlebach PhD**, is trained pharmacist/pharmacologist, internationally respected in scientific, educational, and practical pharmacy-related topics with his broad, inter-professional experience from drug innovation to final drug use in patients accompanied by regulatory science advances. He is currently emeritus Professor with the Division of Clinical Pharmacy and Epidemiology of the Department of Pharmaceutical Sciences at the University of Basel. As university teacher and research member, he supervised, since the early 1990ties, numerous PhD and master's research projects in pharmacokinetics, nanomedicines, clinical nutrition, pharmaceutical and regulatory sciences, resulting in more than 250 peer reviewed publications, including

many pioneering papers and book chapters, including the nanomedicines and Non-Biological Complex Drugs (NBCDs) field. In 2005 he spent a sabbatical leave at Harvard Medical School, collaborating and jointly publishing with Dr David Driscoll, another pharmaceutical expert on parenteral nutrition stability issues. He is an honorary member of the Swiss Association of hospital pharmacists. In 2019 he got an honoris causa doctorate from the Semmelweis University in Budapest and an intense cooperation in Advances in Pharmaceutical Drug Development like the NBCDs resulting a series of international conferences in Budapest. He remains an active member of many professional societies. Aside the academia, Stefan worked as a hospital pharmacist for 25 years and as CSO / Head Regulatory Science in the Swiss and global pharmaceutical industry over almost 12 years. He led the Swiss Pharmacopoeia from 2005-2008 at SwissMedic, the national drug authorization body. From 2010 to 2021 he served as a part-time Head of Therapeutic Products at the Federal Office for National Economic Supply (FONES/BWL), managing the increasing challenges of drug shortages, then during the pandemic, he led the Swiss national logistics working group for the Covid-19 vaccination program at the Federal Office of Public Health (BAG). In the past and up to now Stefan has been an international guest speaker at many important meetings.

# NANOPHARMACEUTICALS / NON-BIOLOGICAL COMPLEX DRUGS (NBCDS) TO IMPROVE DRUG DELIVERY

Stefan Mühlebach

*Basel University, Dept. Pharmaceutical Sciences,  
Division of Clinical Pharmacy & Epidemiology / Hospital Pharmacy  
Spitalstrasse 26, CH-4031 Basel (Switzerland)*

**Introduction:** Drug delivery depends on the physicochemical profile of the API and the related manufacturing and formulation processes. The biopharmaceutics classification system divides drugs into class I-IV related to their solubility (in vitro dissolution) and permeability (drug absorption). Class II includes low solubility / high permeability drugs and counts for around 70% of the drugs showing limited absorption and erratic bioavailability.

**Method:** Nanonization in the API manufacturing allows to increase surface area- to volume-ratio and increases dissolution (nanocrystals). Nanoparticles with defined composition and size can target defined biostructures and impact the intracellular particle / drug uptake and their cellular handling able to change the biodistribution. This is most critical for the very complicated large-molecular structures of biological and non-biological complex drugs (NBCDs).

**Results:** Nanotechnology and nanomaterials are at the forefront for drug innovation and development as shown for example by the novel m-RNA COVID-19 vaccines presented as lipid nano particles (LNP) and successfully launched in the pandemic due to their controlled and targeted intracellular API delivery. These complicated, three-dimensionally structured drugs are highly sensitive to external conditions like temperature or mechanical stress to be kept low and controlled during the long-lasting production process, the storage, and the transport. This was also a major challenge for the vaccine's distribution and mass administration during the pandemic. The demanding and time-intense manufacturing process of such nanopharmaceuticals controls the critical quality attributes essential for their profile and characteristics, not to be completely checked by physicochemical quality control. Therefore, opportunities for and challenges of NBCD nanopharmaceuticals in cancer (liposomal doxorubicin) and iron deficiency treatment (colloidal polymeric iron carbohydrates) for safe and improved drug delivery and treatment including insights in their biological fate and handling are presented.

**Conclusions:** Adapted regulatory evaluation and authorization pathways are needed and in progress for authorization of NBCDs and their follow-on's (similar). They are not yet appropriately established to define their equivalence to the original drug products. In addition, education and knowledge of (hospital) pharmacists are not in place to correctly handle selection and use of these complex drugs.

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# NANOPHARMACEUTICALS: NANOTOXICOLOGICAL CONSIDERATIONS, REGULATORY ISSUES

László Horváth, Béla E. Tóth, Miklós Vecsernyés

*Department of Pharmaceutical Surveillance and Economics, Faculty of Pharmacy,  
University of Debrecen, Rex Ferenc u.1. 4002 Debrecen, Hungary*

The use of nanomaterials (NM) in medical field has increased over the past 10 years, and many different NM systems being utilised in the clinical practice. Many types of polymeric, metallic, lipid based nanoparticles have developed in healthcare, with these generally providing enhanced drug efficacy or therapeutic effect compared to the standard drug treatments. Therefore, the application of nanotechnology in the medical field has a revolutionary impact. Their growing role raises concerns over the safety of NMs during the therapeutic application. Although there is great anticipation surrounding the field of nanomedicine and its influence on the pharmaceutical industry, there is currently very little regulatory guidance in this area. In addition, the most important scientific organizations, including National Institute of Health, USA, European Science Foundation and the European Technology Platform, EU, having differing definitions. Therefore, toxicokinetics, identifications of special hazard on barrier systems, exposure and risk assessment studies of nanomaterials challenges are remaining. The aim of my presentation is to review the rationale challenge behind the appropriate design of the scientific observations with nanomaterial effects on the barrier systems, plasma toxicokinetic and tissue distribution studies. These risk assessment studies using in vitro and in vivo observations help to understand and assess their impact on human health development, and application.

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# TOWARDS OPTIMIZED PREDICTION OF TRANSPORTER-MEDIATED DRUG INTERACTIONS: THE CRL/SOLVO PERSPECTIVE

Péter Tátrai<sup>1</sup>, Tamás Varga<sup>1</sup>, Nóra Szilvász<sup>1</sup>, Csilla Temesszentandrás-Ambrus<sup>1</sup>,  
Zsuzsanna Gáborik<sup>1</sup>

<sup>1</sup>Charles River Laboratories Hungary, H-1117 Budapest, Hungary

**Introduction:** Transporter-mediated drug-drug interactions (DDIs) occur when a drug (the precipitant) alters the pharmacokinetic properties of another drug (the object) by interfering with transporters involved in the object's absorption, distribution, or excretion. Since some transporter-mediated DDIs (tmDDIs) may pose significant clinical risk, regulatory agencies mandate in vitro investigations designed to predict tmDDI liabilities of drugs in development. White papers and regulatory guidance documents recommend standard calculations for extrapolation of in vitro measured data, such as half-maximal inhibitory concentration (IC<sub>50</sub>) of a drug on a given transporter, to anticipated in vivo clinical risk, and define cutoff criteria for follow-up clinical DDI studies. However, the exact parameters of transporter experiments that ensure optimal prediction are subject to constant optimization. Moreover, while drugs as precipitants of drug interactions have been amply discussed, herbal products as potential precipitants have received far less regulatory attention despite their ubiquitous (and poorly controlled) use.

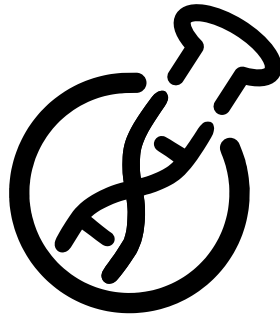
**Results and Conclusions:** Pertinent to the first point, we have demonstrated that short incubation times in transporter inhibition experiments may underpredict interaction risk, and we are currently investigating the impact of in vitro transporter expression levels on measured IC<sub>50</sub> values. To the second point, we have characterized the interactions of two widely applied herbs, *Uncaria tomentosa* and *Zingiber officinale*, with a broad panel of pharmacokinetically relevant transporters, and pinpointed interactions of potential clinical significance.

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# **DRUG DELIVERY THROUGH THE PHYSIOLOGICAL BARRIERS**

**26 APRIL 2025**



# A NEW MODEL TO MONITOR THE TRANSPORT ACROSS THE BLOOD-BRAIN AND BLOOD-TUMOR BARRIER

Thomas Birngruber, Thomas Altendorfer-Kroath

*Institute for Biomedical Research and Technologies (HEALTH), Joanneum Research  
Forschungsgesellschaft m.b.H, Neue Stiftingtalstrasse 2, 8010 Graz, Austria*

**Introduction:** Brain tumors have a poor prognosis and lack effective treatment, as therapeutic agents must overcome the blood-brain barrier (BBB), which represents a major hurdle for drug delivery. Within the tumor, the BBB may be altered to form the blood-tumor barrier (BTB). The BTB is not well defined and ranges from leaky BTB areas that enable diagnosis by contrast-enhanced magnetic resonance imaging to BTB areas with increased efflux pump function that form a very dense barrier for specific substances. This heterogeneous pharmacokinetic behavior of the BTB is a critical factor for the lack of effective brain tumor treatments on the market. Cerebral open flow microperfusion (cOFM) is a sampling technology that allows in-vivo monitoring of transport across the intact BBB. cOFM can remain implanted in the brain tissue for long periods (i.e., months) without causing a foreign body reaction. We aimed to develop an animal model with an atraumatic access to glioblastoma via cOFM.

**Method:** Human glioma U87MG cells were implanted at a well-defined position into the brain of immunodeficient Rowett nude rats by using either cOFM (cOFM group) or a standard syringe (control group). We assessed tumor growth and morphology in both groups.

**Results:** By using cOFM we were able to successfully introduce xenograft into a rat brain, for the first time with an intact BBB. The xenograft glioblastoma developed at the interface between the cOFM probe and the surrounding brain tissue. The tumor tissue growing around the cOFM probe was unaffected by the presence of the cOFM probe. The success rate of glioblastoma development in the cOFM group was high (>70%). The mature cOFM-induced tumors (20-23 days after cell-implantation) resembled the syringe-induced ones and showed typical features of human glioblastoma.

**Conclusions:** Our cOFM-supported xenograft model allows an atraumatic access into the tumor and therefore the possibility to monitor the behavior and the changes in BTB throughout the development and metamorphosis of a glioblastoma. Substance transport through both barriers can be simultaneously measured in the same animal by placing cOFM probes in both hemispheres of the brain. One probe is measuring transport through the intact BBB, while the other probe is measuring transport through the BTB. Our model also allows for the investigation of the BTB in different tumor stages to facilitate an effective development and testing of brain cancer treatments.

# ANALOG OF KYNURENIC ACID DECREASES TAU PATHOLOGY BY MODULATING ASTROGLIOSIS IN RAT MODEL FOR TAUOPATHY

Petra Majerova, Krutika Khiratkar, Andrej Kovac

*Institute of Neuroimmunology, Slovak Academy of Sciences, Bratislava, Slovakia*

**Introduction:** Kynurenines have immunomodulatory and neuroactive properties and can influence the central nervous system. Previous studies showed the involvement of the kynurenines in the pathogenesis and progression of neurodegenerative disease. In neurodegenerative disorders, including tauopathies, the tryptophan metabolism is shifted toward neurotoxic agents and the reduction of neuroprotectant products. Astrocyte-derived kynurenic acid serves as a neuroprotectant. However, systemic administration of kynurenic acid is not effective because of low permeability across the blood-brain barrier (BBB). We used a kynurenic acid analog with similar biological activity but higher brain permeability to overcome BBB limitations.

**Methods:** In the present study, we used amide derivate of kynurenic acid N-(2-N, N-dimethylaminoethyl)- 4-oxo-1 H-quinoline-2-carboxamid (KYNA-1). We administered KYNA-1 for three months to tau transgenic rats SHR-24. We used immunohistochemistry and biochemical analysis to demonstrate and analyze the effect on tau pathology and activation of glial. We developed a sensitive analytical method to quantify metabolites of tryptophan metabolism in biological samples.

**Results:** KYNA-1 was not toxic to rats after a chronic three-month administration. When chronically administered, KYNA-1 reduced hyperphosphorylation of insoluble tau in the brains of transgenic rats. Noteworthy, the plasma total tau was also reduced. We determined that the effect of KYNA-1 on tau pathology was induced through the modulation of glial activation. KYNA-1 inhibited LPS induced activation of astrocytes and induced transformation of microglia to M2 phenotype.

**Conclusion:** Altogether our results strongly suggest that chronic administration of the synthetic analog of kynurenic acid (KYNA-1) reduces tau phosphorylation and astrogliosis in a transgenic rat model for tauopathies. The analog reversed LPS- induced inflammatory changes in glial cell cultures and shifted the tryptophan metabolism in the neuroprotectant direction. Neuroprotective analogs KYNA-1 can serve as a new and effective potential therapeutic approach for tauopathies.

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# **TARGETING THE BRAIN WITH GENE THERAPY VECTORS: EVALUATING THE SAFETY AND EFFICACY OF DELIVERY ROUTES ACROSS PHYSIOLOGICAL BARRIERS**

**Dániel Hillier**

*Pázmány Péter Catholic University, Faculty of Information Technology and Bionics,  
Práter u. 50/a, 1083 Budapest, Hungary*

Modulating brain function via genetic approaches in non-mouse models remains challenging due to the limited availability of transgenic lines. Gene therapy vectors, particularly AAVs, offer a means to target specific cell populations; however, their efficacy depends on vector tropism and the ability to overcome biological barriers such as the blood-brain barrier, the eye-brain barrier, and the blood-CSF barrier, as well as effectively reach the brain via the cerebrospinal fluid (CSF). Furthermore, achieving stable and safe access to brain function—for instance, via opto- and chemogenetic modulation—requires consistent transgene expression with minimal immune activation.

We evaluated different delivery routes and gene therapy constructs to achieve long-term, safe, and stable transgene expression in the brain. To assess functional modulation, we performed long-term optical imaging in animal cohorts over several weeks, examining labeling efficacy, stability of activity readouts, and local as well as systemic immune responses. Our findings reveal nonlinear relationships among dose, expression levels, and immune activation.

This work establishes an optimized gene therapy delivery strategy in large-brained species, enabling stable, long-term modulation of brain function while minimizing immune responses.

# BRAIN PENETRATION PREDICTION METRICS IN CNS DRUG DISCOVERY, IN-SILICO MODELL DEVELOPMENT FOR BBB PENETRATION

János Éles, Balázs Krámos, Mónika Vastag, Attila Halász, Ottilia Balázs

*Gedeon Richter Pharmaceuticals, Research and Development Directorate, Chemistry Division,  
Gyömrői út 19-21, 1108 Budapest, Hungary*

**Introduction:** Achievement of appropriate blood-brain barrier penetration is often considered a significant obstacle in CNS drug discovery. A clear understanding of the physicochemical and structural properties of CNS penetrant molecules could assist the research of diseases such as depression, anxiety, stress disorder, Alzheimer's disease, Parkinson's disease or brain cancer which cost trillions of dollars for their current treatment. Against the numerous and challenging issues in CNS drug discovery, pharmaceutical companies reprioritize their drug discovery efforts and turn more attention to the CNS disease field. Numerous analyses of CNS drugs resulted in the evolvement of property metrics to support the lead selection and the lead optimization processes.

**Results:** As part of our effort to increase the efficiency of our CNS drug research and to move our medicinal chemistry design to a higher probability space for success in identifying brain penetrant compounds, we embarked a detailed study in the property space for a collection of compounds designed and synthesized in our aminergic GPCR research program. We focused on understanding the relationship between certain physicochemical properties and Pgp substrate liability of a set of compounds. Our in-house built in-silico prediction model provided us guidance for the design of molecules in a property space with increased probability of success and may lead to the identification of brain penetrant compounds.

**Conclusions:** Our in-silico model provides us a holistic assessment of the BBB penetration property of a designed compound, and we believe the algorithm will provide a new way of evaluating ideas and impact prioritization. Ultimately our goal is to move our compound design to a space of higher probability of success to increase speed in the identification of leads and candidates.

# EXAMINATION OF VIRAL PEPH3 PEPTIDE-FUNCTIONALIZED NANOPARTICLES ON A CULTURE MODEL OF THE BLOOD-BRAIN BARRIER

Anikó Szecskó<sup>1,2</sup>, Mária Mészáros<sup>1</sup>, Vera Neves<sup>3</sup>, Marco Cavaco<sup>3</sup>, Beatriz Simões<sup>3</sup>, Catarina Chaparro<sup>3</sup>, Miguel A.R.B. Castanho<sup>3</sup>, Mária A. Deli<sup>1</sup>, Szilvia Veszélka<sup>1</sup>

<sup>1</sup>*Biological Barriers Research Group, Institute of Biophysics,  
HUN-REN Biological Research Centre, Szeged, Hungary*

<sup>2</sup>*Doctoral School of Biology, University of Szeged, Szeged, Hungary*

<sup>3</sup>*Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Portugal*

**Introduction:** Nanoparticles (NPs) are promising new tools to increase the transfer of drugs across the blood-brain barrier (BBB) to the CNS. With appropriate ligands, vesicular NPs are suitable for targeted drug delivery across the BBB. The aim of this study was to investigate the PepH3 peptide, isolated from the capsid protein of Dengue virus as a targeting ligand of NPs to elevate the cargo penetration across the BBB.

**Method:** In our experiments, we prepared PepH3-targeted NPs loaded with Texas-Red labelled bovine serum albumin (TR-BSA) or single-domain antibody (sdAb) against amyloid beta peptide as cargo. The physico-chemical properties of NPs, such as particle size, polydispersity index and surface charge were measured by dynamic light scattering. The encapsulation efficiency was detected by spectrofluorimeter or western blot. The effect of PepH3-targeted NPs on the viability of primary rat brain endothelial cells was monitored by impedance measurement. The cellular uptake and co-localization of NPs cargo with endoplasmic reticulum (ER), Golgi apparatus and lysosomes were visualized by confocal microscope. The cellular internalization, mechanisms of cellular uptake, and the penetration of NPs across the culture model of the BBB was quantified by spectrofluorimeter.

**Results:** The average diameter of non-targeted and N-PepH3 particles was between 98-207 nm, respectively. NPs have a slightly negative surface charge and a relatively narrow size distribution. The encapsulation efficiencies of non-targeted and PepH3-targeted TR-BSA-loaded NPs were 32 and 24 %, respectively, and for sdAb-loaded NPs they were 93 and 68 %, respectively. PepH3 as a targeted ligand successfully increased cellular internalization of TR-BSA cargo at each time point compared to the non-targeted group. After cellular uptake, TR-BSA colocalized with ER and Golgi and limited amounts of lysosomes. Uptake of the TR-BSA cargo was an energy- and surface charge-dependent process and was partially mediated by endocytosis. The transfer of PepH3-targeted NPs containing sdAb cargo after 24 h of incubation had significantly higher penetration through the BBB model compared to non-targeted NPs.

**Conclusions:** Our results demonstrated that PepH3 is a good candidate to be used as a peptide for targeted brain delivery of therapeutic biomolecules.

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# ADVANCED DRUG DELIVERY SYSTEMS FOR THE IMPROVEMENT OF BIOAVAILABILITY AND PATIENT-CENTRICITY

István Antal, Milena Lengyel, Zsófia Kohod, Bálint Basa, Nikolett Kállai-Szabó

*Semmelweis University Department of Pharmaceutics, Hőgyes 7, 1092 Budapest, Hungary*

**Introduction:** Today, the development of new dosage forms is of particular importance as they create new opportunities to improve the safety and efficacy of drug therapy. A well-constructed formulation with advanced excipients is also a drug delivery system that can increase efficacy and/or reduce side effects through innovative technological solutions.

The release profile and physiological environment is based on the structure, and in many cases also the integrity, of the dosage form, which determines the pharmacokinetic profile (e.g. dissolution and absorption). The specific formulation or manufacturing technology may result in more uniform efficacy and/or better tolerability, as well as other properties that aid compliance and adherence.

The pharmaceutical formulation is expected to provide the appropriate level of activity, onset, and duration of action, but there are also challenges about special considerations for certain patient groups (e.g. elderly or children) and for people with certain medical conditions (e.g. difficulty swallowing, mental or physical conditions). Innovative pharmaceutical technologies can ensure the desired pharmacokinetic profile, appropriate bioavailability, and improved dosing regimens.

**Results and Conclusions:** Multiparticulate systems such as microparticles, microspheres, nanocarriers show various therapeutic advantages for patient-centric drug delivery based on their structural and functional capabilities. The different structures allow the possibility of tailored drug release mechanisms and modulating optimized pharmacokinetic profiles.

The right dosage form is an important prerequisite for successful therapy. Drug Delivery Systems may allow more favorable dosing and dosage regimens while promoting patient cooperation and thus the effectiveness.

# NANOFIBER-ENCAPSULATED EXTRACELLULAR VESICLES: A NOVEL APPROACH FOR DRUG DELIVERY AND STABILITY ENHANCEMENT

Romána Zelkó <sup>1</sup> and Adrienn Kazsoki <sup>1</sup>

<sup>1</sup>*Semmelweis University, Faculty of Pharmacy, University Pharmacy Department of Pharmacy Administration, Hőgyes E. u. 7-9, 1092 Budapest, Hungary*

**Introduction:** Extracellular vesicles (EVs) have emerged as promising candidates for drug delivery due to their biocompatibility and ability to cross biological barriers. However, their storage and stability present challenges for therapeutic applications. To investigate the potential of incorporating EVs into nanofibers as a method for enhancing stability and controlled release of therapeutic agents, curcumin was selected as a model drug.

**Method:** EVs were isolated from HEK293 cells and loaded with curcumin. These drug-loaded EVs were then incorporated into polyvinyl alcohol (PVA) nanofibers using electrospinning. The stability and release characteristics of the EV-loaded nanofibers were evaluated using flow cytometry, confocal laser scanning microscopy, and dissolution studies.

**Results:** EV-loaded nanofibers demonstrated improved stability compared to free EVs. Curcumin-loaded large EVs (lEVs) exhibited a biphasic release profile when incorporated into PVA nanofibers, suggesting a more controlled release mechanism compared to small EVs (sEVs). The size of the EVs significantly influenced the curcumin loading efficiency and release characteristics.

**Conclusions:** Incorporating EVs into nanofibers presents a promising approach for preserving EV stability and enabling controlled drug release. This method addresses challenges in EV storage and administration, paving the way for future therapeutic applications. However, further research is needed to optimize drug loading efficiency and understand the underlying mechanisms of EV-based drug delivery systems.

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# MICROSPHERES AND MICROCAPSULES AS MULTIPARTICULATE DOSAGE FORMS FOR OPTIMIZED DRUG DELIVERY

Miléna Lengyel<sup>1</sup>, Nikolett Kállai-Szabó<sup>1</sup>, Christian Fleck<sup>1</sup>, Lilla Kóró<sup>2</sup>, Zsófia Szabó<sup>2</sup>,  
András Laki<sup>3</sup> and István Antal<sup>1</sup>

<sup>1</sup>*Semmelweis University, Department of Pharmaceutics, Hőgyes E. str. 7,  
1092 Budapest, Hungary*

<sup>2</sup>*Semmelweis University, Faculty of Pharmaceutical Sciences, Üllői str. 26,  
1085 Budapest, Hungary*

<sup>3</sup>*Pázmány Péter Catholic University, Faculty of Information Technology and Bionics,  
Práter u. 50/a, 1083 Budapest, Hungary*

Multiparticulate dosage forms are systems containing small particles as individual drug-releasing units, which can be used in a variety of pharmaceutical forms: tablets, capsules, extended-release granules, topical dosage forms, parenteral suspensions, depot injections. The size range of the particles constituting a multi-unit system is very wide, from 1 to 1000 µm, depending on the intended use.

Systems containing coated multiparticles (pellets, microcapsules, microspheres) have several advantages. Above the protection of the active agent from the environment (oxidation, temperature, pH) and the body from the irritating effects of the active ingredients, the small units can control the release of the active substance individually to achieve a targeted effect, or even the initial and maintenance dose can be administered in a single dosage form. Further advantages are their scalable dosing, homogenous distribution, and the avoidance of the dose dumping on the damage of a single unit by halving the dosage form. Depending on the formulation the drug release may also be controlled by an external stimulus (chemical, electrical, magnetic, osmotic or thermal).

The presentation aims to show the wide variety of microparticulate dosage forms, focusing mainly on the production and the examination processes of hydrogel particles and pellet preparations. The production of gel-state microparticles containing natural polymers by simple coacervation or complex coacervation (e.g. Büchi B-390 in a dual-atomisation micro-encapsulation device) is influenced by droplet formation and gelation. The optimisation of factors like the concentration of coacervation medium, gelation time, gel-forming polymer feed rate, apparatus parameters (frequency, voltage, distance of coacervation medium from the nozzle), addition of surfactants have a significant effect on the product.

The examination of the morphological, physico-chemical properties of the particles include the observation of the gelation process, and in common with solid pellet particles the study of the swelling and drug release of solid units in different dissolution media can be followed by microfluidic processes.

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# THE APPLICATION OF CYCLODEXTRIN POLYMERS IN GENE THERAPY

Ágnes Rusznyák<sup>1</sup>, Virág Dajka<sup>1</sup>, Milo Malanga<sup>2</sup>, Ildikó Bácskay<sup>3</sup>, Ferenc Fenyvesi<sup>1</sup>

<sup>1</sup>*Department of Molecular and Nanopharmaceutics, Faculty of Pharmacy,  
University of Debrecen, Hungary*

<sup>2</sup>*CarboHyde Zrt., Budapest, Hungary*

<sup>3</sup>*Department of Pharmaceutical Technology, Faculty of Pharmacy,  
University of Debrecen, Hungary*

**Introduction:** Nowadays, RNA-based therapies play an increasingly important role in the treatment of various diseases. Due to the large molecular size and polyanionic nature of RNA, it is difficult to transfect into cells [1]. To solve this problem, many carrier systems are under development or available. These delivery systems are usually based on liposomes or polymers, such as cyclodextrin polymers [2]. These molecules are able to deliver macromolecules, while their monomer derivatives are widely used excipients to increase the solubility and bioavailability of lipophilic molecules. In our work, we aimed to investigate the RNA carrying capacity of a positively charged cyclodextrin polymer (Q polymer) and polyethyleneimine (P polymer), to examine the properties of the polymers and the formulated polyplexes. Besides, we aimed to investigate the cellular internalization and the intracellular effects of polyplexes via gene silencing or expression.

**Method:** The cytotoxic effect of the polymers was measured by MTT method on HeLa cells. The properties of the formulated polyplexes were investigated using dynamic light scattering technology (DLS) and zeta potential measurements. The cellular internalization and the intracellular effects of the polyplexes were investigated by confocal or fluorescence microscopy and flow cytometry.

**Results:** The polyethyleneimine was more cytotoxic than the cationic cyclodextrin polymer. According to the DLS and zeta potential measurements both polymer were able to form polyplexes with siRNA and mRNA, but based on the gel electrophoresis, the cyclodextrin polymer is able to form a stronger polyplex. Polyplexes formulated with Q polymer were able to enter the cells, while these formulated with P polymer were bound to the cell membrane. Polyplexes were influenced both the GAPDH and green fluorescent protein (GFP) expression, but the increasing concentration of P polymer was cytotoxic.

**Conclusions:** In summary, we have successfully formulated cyclodextrin polymer-based RNA carrier system. Polyplexes formulated with different polymers showed different cellular internalization. Polyplexes formulated with Q polymer were taken up by cells and were influenced the expression of proteins.

**References:** [1] Kanasty, R.; Dorkin, J.R.; Vegas, A.; Anderson, D. Delivery materials for siRNA therapeutics. *Nat. Mater.* 2013, 12, 967–77, doi:10.1038/nmat3765.

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# THE EVOLUTION AND RECENT ADVANCES OF 3D-PRINTED DRUG DELIVERY SYSTEMS

Petra Arany<sup>1</sup>, Pálma Fehér<sup>1</sup>, Zoltán Ujhelyi<sup>1</sup>, Prof. Ildikó Bácskay<sup>1</sup>

<sup>1</sup>University of Debrecen, Faculty of Pharmacy, Department of Pharmaceutical Technology,  
Rex Ferenc street 1, H-4002, Debrecen

**Introduction:** Three-dimensional (3D) printing is one of the most advancing technology in the manufacturing of pharmaceuticals. This layer-by-layer process enables fast and cost-effective creation of personalized drug products. The first FDA-approved 3D-printed drug, Spritam®, an orally disintegrating tablet for treating epileptic seizures, was approved in 2015. Since then, the amount of researches in this field has expanded dramatically, with numerous studies exploring different manufacturing methods. (1)

**Method:** A systematic review was made about the biggest innovations based on the type of the manufactured drug delivery system. In one study, diclofenac sodium-loaded implants were produced using Fused Deposition Modeling (FDM) 3D printing with different polymers. The material structure, cell viability, and dissolution properties of the tablets were assessed. (2) 3D-printed vaginal rings were made from TPU (Thermoplastic Polyurethane) and filled with metronidazole or chloramphenicol gel for the treatment of bacterial vaginosis. The study evaluated the material structure, dissolution profile and biocompatibility of these rings. (3)

**Results:** In the review more than 150 articles were analyzed and sub grouped, even rare drug delivery systems were described. The first experiment demonstrated that the FDM-printed drug-loaded samples maintained the stability of the active pharmaceutical ingredient (API) and printing parameters played a crucial role in optimizing the dissolution profile. All samples were biocompatible, suggesting that they are suitable for further in vivo and human studies. The second experiment revealed that the TPU-based vaginal rings filled with API-containing gels showed no cytotoxic effects and exhibited a slow release profile of the active ingredients within the first 24 hours.

**Conclusions:** In conclusion, 3D printing represents an exciting and cutting-edge technology in drug manufacturing, which is about to revolutionize the healthcare industry. Over the last two decades, many research groups have worked to create different drug dosage forms to enhance the safety, efficacy, and tolerability of medications while providing personalized treatments for patients.

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(2) Arany P et al. 2020. *Molecules*. 25(24): 1-31  
(3) Arany P et al. 2019. *Pharmaceutics*. 11(6):1-23

# FORMULATION OF PATIENT-CENTRIC AND MULTIPARTICULATE DOSAGE FORMS BY 3D PRINTING

Bálint Basa<sup>1</sup>, Nikolett Kállai-Szabó<sup>1</sup>, Emese Balogh<sup>1</sup>, Ádám Tibor Barna<sup>1</sup>,  
Gábor Ujvári<sup>1</sup>, Zsófia Kohod<sup>1</sup>, Richárd Levente Kozma<sup>1</sup>, István Antal<sup>1</sup>

<sup>1</sup>*Semmelweis University, Faculty of Pharmaceutical Sciences, Department of Pharmaceutics,  
Hőgyes Endre u. 7., 1092 Budapest, Hungary*

**Introduction:** The research activity towards additive manufacturing in the pharmaceutical industry has been increased in the following years, as this technology offers not just the preparation of functionalized micro- and nanostructures, but also enables small-batch production which are inevitable from the viewpoint of personalized medicine. Among the recent trends of pharmaceutical research and development the utilization of multi-unit dosage forms can also be found as possible strategy to broaden patient centricity and enhance cooperation and adherence.

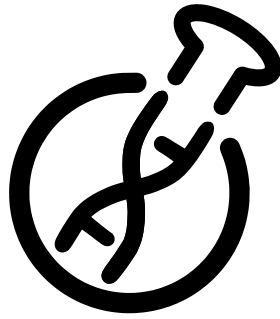
**Method:** In the first phase of this study, the application opportunities of Fused Deposition Modeling (FDM) printing and water soluble polymer (poly(vinyl alcohol)- PVA) was investigated. The Computer Aided Design formed and printed solid drug delivery devices were equipped with an inner reservoir and various numbers of active ingredient eluting pores to ensure controlled drug delivery. The second phase of the research aimed to screen the possible conventional pharmaceutical excipients which can be formulated into 3D printing material with suitable physical and chemical characteristics. The utilized device was a single-screw hot-melt extruder. This scientific work also focused on exploring the possible formulation strategies of multiparticulate systems consisting of versatile units capable of carrying active ingredients.

**Results:** During the investigations biocompatible 3D printed carriers were formulated and based on the biorelevant erosion- and dissolution tests it can be stated that PVA is a suitable biodegradable candidate for the future. The screening process highlighted, that well-known pharma excipients can be utilized as 3D printing starting materials in case of FDM printing. Moreover, microparticles with well-defined dimensions and good reproducibility were also performed with additive manufacturing, paving the way for the further studies in this particular field.

**Conclusions:** Assessing all the results, it can be concluded, that the utilization of 3D printing makes possible to formulate biodegradable, soluble carriers and even multiparticulate dosage forms with various liberation profiles in order to personalize the pharmaceutical therapy of the patients. The digital pharmaceutical technology and CAD design promotes the patient-centric perspective of the personalized medication.

**References:** Basa B et al. 2021. *Materials*, 14, 1350.

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**DRUG DELIVERY  
THROUGH  
THE PHYSIOLOGICAL  
BARRIERS**

**POSTERS**



# PREPARATION AND CHARACTERIZATION OF FREEZE-DRIED $\gamma$ CD-MOF/IBU COMPLEXES FOR DIFFERENT ADMINISTRATION ROUTES

Anett Motzwickler-Németh<sup>1</sup>, Buket Büyüksandıcı<sup>2</sup>, Ildikó Csóka<sup>1</sup>, Rita Ambrus<sup>1</sup>

<sup>1</sup>*Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged, Hungary*

<sup>2</sup>*Institute of Pharmaceutical Technology and Regulatory Affairs,  
Süleyman Demirel Üniversitesi, Türkiye*

**Introduction:** The clinical application of ibuprofen (IBU), a widely used NSAID for pain, inflammation, and fever, is limited by poor aqueous solubility (1) and side effects. In addition to its low solubility, the first-pass metabolism further reduces the bioavailability and effectiveness. As a result, doses are often increased up to tenfold (2), amplifying the risk of adverse effects. These challenges underscore the need to enhance IBU's solubility and explore alternative routes of administration.

**Method:** This preformulation study focused on the preparation and characterization of high-loaded  $\gamma$ -cyclodextrin-based metal-organic frameworks ( $\gamma$ CD-MOFs) as potential carriers for IBU. Particle size, crystallinity, intermolecular interactions, and polarity were investigated using characterization techniques such as Laser Diffraction, Differential Scanning Calorimetry (DSC), Fourier-Transform Infrared Spectroscopy (FTIR), X-Ray Powder Diffraction (XRPD) and Optical Contact Angle (OCA) measurements. Through dissolution studies in simulated nasal electrolyte solution (pH 5.6), artificial saliva (pH 6.4), artificial lung media (pH 7.4), intestinal media (pH 6.8) and gastric acid (pH 1.2) the applicability of these formulations for different routes of administration was assessed.

**Results:** The preformulation exhibited a spherical shape with a highly wrinkled surface as shown by the SEM picture. Laser Diffraction measurements revealed an inhomogeneous particle size distribution since the  $d(0.1)$ ,  $d(0.5)$  and  $d(0.9)$  values were  $2.1\pm0.1$ ,  $14.2\pm1.0$  and  $47.5\pm5.5$ , respectively, with a span value of  $3.2\pm0.6$ . The absence of IBU's melting point on the DSC curve suggests complex formation with  $\gamma$ CD-MOFs or potential amorphization. XRPD analysis confirmed significant crystalline structure changes, indicating successful complexation and a new molecular arrangement. FTIR further validated the incorporation of IBU into the complexes. Wettability studies demonstrated a significant enhancement in the hydrophilicity of the  $\gamma$ CD-MOF/IBU complex, as indicated by a reduced water contact angle of  $18.92^\circ$  compared to  $66.36^\circ$  for raw IBU. Dissolution tests demonstrated improved performance in lung media, artificial saliva, simulated nasal fluid, and intestinal media, highlighting the potential for alternative administration routes.

**Conclusions:** These findings demonstrate how  $\gamma$ CD-MOF-based carriers can optimize formulation parameters to enhance the solubility of IBU thereby increasing its bioavailability. This establishes a foundation for the development of alternative drug delivery systems that improve efficacy while reducing side effects. Further research is necessary to investigate these formulations and assess their applicability across different routes of administration.

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# NOVEL EXCIPIENT FORMULATIONS FOR EFFECTIVE LUNG DELIVERY OF NSAIDS

Zsófia Ilona Pizsman<sup>1</sup>, Rita Ambrus<sup>1</sup>, Petra Party<sup>1</sup>

<sup>1</sup>*Institute of Pharmaceutical Technology and Regulatory Affairs, Faculty of Pharmacy,  
University of Szeged, Szeged, Hungary*

**Introduction:** Chronic lung diseases are among the leading causes of death worldwide. In the treatment of these diseases, non-steroidal anti-inflammatory drugs (NSAID) can be effective. It is advantageous to deliver the active pharmaceutical ingredient (API) directly to the lungs, as this preserves the efficacy of therapy at lower doses. Of the dosage forms designed for pulmonary delivery, our research has focused on the development of dry powder inhalation (DPI) formulations. We have previously developed an ibuprofen containing innovative excipient formulation alongside a modern manufacturing protocol, which we aim to further investigate. For this development, we have used two model NSAIDs, meloxicam (MX) and its water-soluble salt, meloxicam potassium (MXP). The final DPIs were expected to have a spherical shape, micro-sized particles, fast drug release and good aerodynamic properties.

**Method:** The developed excipient combination contained mannitol, Poloxamer-188 polymer and leucine. The DPI systems were prepared by spray drying, preceded by solution preparation for MXP and wet grinding for MX to reduce particle size. In the final product, particle size was determined by laser diffraction, shape by scanning electron microscopy (SEM), crystallinity by powder X-ray diffraction (XRPD) and differential scanning calorimetry (DSC), in vitro aerodynamic properties by Andersen cascade impactor (ACI) and Spraytec® apparatus, and in vitro dissolution in artificial lung fluid.

**Results:** We successfully achieved the proper particle size for pulmonary delivery (between 3 and 6 µm). According to the SEM investigation, the particles showed advantageous spherical shape. From the XRPD and DSC results we suspected a partial amorphization in the spray-dried samples, which may contributed to the greater dissolution profiles. During the in vitro dissolution tests more than 90% of MX released from the powder within the first 10 minutes, therefore achieving an improvement compared to the physical mixtures. Due to its good water-solubility, MXP showed similarly great dissolution from both the spray-dried formulations and the physical mixtures. Results from the Andersen cascade impactor for the samples containing MXP showed higher deposition on the upper stages, while the MX samples were more evenly distributed across stages. The best products exhibited an average aerodynamic diameter of less than 3 µm, a fine particle fraction greater than 60%, an emitted fraction over 95%, and thus effective lung deposition. Based on the particle size analysis by Spraytec®, the MX containing samples were suitable for lung targeting.

**Conclusions:** Overall, based on the studies with different active ingredients, it can be concluded that the previously developed manufacturing protocol and excipient system can be applied in the development of different API containing formulations for pulmonary delivery.

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Szabó-Révész P. 2018. *Drug Discov Today: Technol* 27:87-93

# THERMORESPONSIVE IN SITU GELS FOR ENHANCED OCULAR DRUG DELIVERY

Boglárka Szalai, Orsolya Jójárt-Laczkovich, Mária Budai-Szűcs

*Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged,  
Szeged, Hungary*

**Introduction:** Ocular inflammatory conditions affect millions worldwide. Dexamethasone (DXM) is a potent corticosteroid used to treat these conditions. However, effective drug delivery across the ocular barrier remains a major challenge in pharmaceutical research. Conventional eye drops face several limitations; less than 5% of the drug penetrates the eye as the drug is rapidly removed from the eye surface [1]. This study aimed to formulate thermoresponsive in situ gelling systems to enhance solubility, retention time and permeability of DXM [2].

**Method:** DXM was solubilized by hydroxypropyl- $\beta$ -cyclodextrin (HPBCD). The thermoresponsive component of the formulations was Poloxamer 407 (P407) and mucoadhesive polymers were also incorporated in them to increase mucoadhesion. Two in vitro (corneal-PAMPA and HCE-T cell line) permeability tests and an ex vivo porcine eye study were performed to evaluate the permeability of the gels, while biocompatibility was also assessed on the HCE-T cell line.

**Results:** The optimized in situ gel formulation significantly improved corneal permeability compared to a DXM suspension and the solution of the DXM-HPBCD inclusion complex. The ex vivo study suggested that HPBCD may facilitate the drug penetration into the aqueous humor. The combination of HPBCD and thermoresponsive in situ gels facilitated prolonged retention and enhanced permeability. Furthermore, the formulation showed no cytotoxic effects on the HCE-T cell line.

**Conclusions:** These findings underscore the potential of thermoresponsive in situ gels to overcome ocular physiological barriers, providing an innovative approach for improving the efficacy of topical ophthalmic therapies.

**References:** [1] Jünemann A.G.M. et al. 2016. Ophthalmol J. 1(1), 29–35.

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## Acknowledgement

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# DOUBLE-NEEDLE ELECTROSPINNING OF ORODISPERSIBLE MEMBRANES LOADED WITH DICLOFENAC

Luca Éva Uhljar, Tekla Jáger, Rita Ambrus

*University of Szeged, Faculty of Pharmacy, Eötvös u. 6., 6720 Szeged, Hungary*

**Introduction:** Electrospinning (ES) is an electrohydrodynamic phenomenon in which the fibers are formed by drawing out a polymer jet under a high electric field. ES is the most common process for fine-fiber production as it is a simple, cost-effective, but a versatile and practical method. Usually, nanofibers are produced by ES but in cases where the average fiber diameter is around 1000 nanometers, it is more appropriate to talk about microfibers. Microfibers can be used as various drug-delivery systems, e.g., orodispersible membranes. In this case, the use of a BCS Class I drug and a water-soluble polymer, and the large surface area of the microfibers ensure rapid drug delivery.

Our purpose was to create an orodispersible, polymer-based, NSAID-containing membrane that can be an alternative for pain-killer tablets.

**Method:** Diclofenac-loaded nanofibers were prepared by a double-needle ES setup. The second needle was installed to increase the production rate. Polyvinyl pyrrolidone (PVP) was used as a matrix-forming polymer. The morphology was examined by scanning electron microscopy (SEM). The drug content was measured by UV spectroscopy. The in vitro disintegration was tested by two methods: artificial saliva and simulated tongue. Moreover, the in vitro dissolution was also executed via two methods: in artificial saliva and biorelevant gastric medium.

**Results:** The ES of the microfibrinous membrane was successful. The use of the second needle doubled the productivity of the ES process. The SEM images showed that homogenous, fibrous structures were produced. The average fiber diameter was around 1 micron. The real drug content approached the theoretical 10 w/w%. The disintegration of the microfibers occurred in seconds, and the complete drug release in artificial saliva took around 10 minutes. In the biorelevant gastric medium, the microfibers showed superior dissolution properties.

**Conclusions:** In accordance with our purpose, DIC-loaded microfibers were produced. The production rate was increased by using a double-needle ES setup. The microfibrinous membrane was proved to be a proper orodispersible drug delivery system for DIC. In this way, these membranes could be an alternative for DIC-containing tablets.

# EPIOCULAR™ TIME-TO-TOXICITY – A TEST METHOD FOR SUBCATEGORIZATION OF EYE IRRITANTS

Emiy Reis<sup>1</sup>, Lenka Hudecova<sup>1</sup>, Jan Markus<sup>1</sup>, Silvia Letasiova<sup>1</sup>, Yulia Kaluzhny<sup>2</sup>,  
Els Adriaens<sup>3</sup>, Mitch Klausner<sup>2</sup>

<sup>1</sup>MatTek In Vitro Life Science Laboratories, Mlynske Nivy 73, 82105 Bratislava, Slovakia

<sup>2</sup>MatTek Corporation, 200 Homer Ave, Ashland, MA, USA

<sup>3</sup>Adriaens Consulting BVBA, Bellemdorpweg 95, 9981 Adler, Belgium

**Introduction:** In 2015, an OECD TG 492 was accepted and validated for the use of in vitro ocular tissue models. Initially, this TG only allowed for distinguishing between substances and mixtures not requiring classification and those that must be labeled for eye irritation or serious eye damage. Further specification of eye irritation severity was not included in the TG. More recently, an OECD TG 492B was accepted, which allows for distinguishing between chemicals that: a) do not require labeling for serious eye damage or eye irritancy (No Cat), b) cause serious eye damage (Cat 1), and c) are eye irritants (Cat 2) according to the UN GHS ocular hazard categories.

**Methods:** A new testing strategy was developed based on the results from two studies, CON4EI and ALT4EI projects. A robust final set of 144 reference chemicals – 78 liquids and 66 solids – was obtained. Using this data set, the EpiOcular™ time-to-toxicity test method was developed for eye hazard identification of liquid and solid chemicals according to UN GHS.

**Results:** The results confirmed the new testing strategy. The performance criteria, established by the OECD expert group overseeing OECD TG 492B, were met for all 144 chemicals. Overall, the new test method correctly predicted: 76.8% of Cat 1 (N=55), 61.9% of Cat 2 (N=42), and 81.2% of No Cat (N=47) test articles.

**Conclusion:** The EpiOcular™ time-to-toxicity test method is a novel approach for subcategorizing both liquid and solid compounds. The prediction models for liquids and solids are capable of distinguishing substances and mixtures into No Cat, Cat 2, and Cat 1 categories.

# BIOMEMBRANE-ON-A-CHIP DEVICE FOR MONITORING DRUG DIFFUSION

András József Laki<sup>1,2</sup>, Dorottya Kocsis<sup>1</sup>, Mária Laki<sup>1</sup>, and Franciska Erdő<sup>1</sup>

<sup>1</sup>Pázmány Péter Catholic University, Faculty of Information Technology and Bionics,  
Práter u. 50/a, Budapest, 1083, Hungary

<sup>2</sup>Semmelweis University, Department of Biophysics and Radiation Biology,  
Tűzoltó u. 37-47, Budapest, 1094, Hungary

**Introduction:** The Biomembrane-on-a-Chip device represents a universal platform for evaluating transmembrane drug diffusion across various materials [1]. This innovative microfluidic system enables precise and reproducible assessment of drug transport mechanisms, providing a valuable tool for pharmaceutical research and development. By mimicking physiological barriers, the device facilitates monitoring of diffusion processes and enhances the understanding of drug permeability in different formulations.

**Methods:** A patented device was designed, prototyped, and validated using a reference system. The experimental setup incorporated a biomimetic membrane model to simulate physiological conditions [2]. Additionally, computational fluid dynamics (CFD) simulations were performed to optimize diffusion parameters mathematically. The prototype was tested with  $\alpha$ -Aminophosphonates (APPs) to evaluate drug release and penetration across dermal barriers under controlled conditions.

**Results:** Experimental trials demonstrated that the release and skin penetration of the tested APPs varied based on their molecular properties [3]. The unsubstituted 1a molecule exhibited the highest permeability, while 4-MePh and 4-ClPh derivatives showed limited transdermal diffusion. The differences in transdermal delivery efficiency among the APPs were attributed to their lipophilicity.

**Conclusions:** The Biomembrane-on-a-Chip device successfully demonstrated its capability to assess drug diffusion through physiological barriers. The study highlighted significant differences in penetration efficiency among APPs, primarily influenced by molecular properties and formulation characteristics. Future research should focus on elucidating specific transport mechanisms involved in transcellular penetration [4]. This device offers a promising approach for optimizing drug formulations and improving transdermal drug delivery strategies.

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# DEVELOPMENT OF FORMULATIONS BASED ON SALVIA OFFICINALIS AND INVESTIGATION OF THEIR EFFECTS IN VITRO AND IN VIVO

Pálma Fehér<sup>1</sup>, Krisztina Bodnár<sup>1</sup>, Liza Józsa<sup>1</sup>, István Lekli<sup>2</sup>, Fruzsina Nacsá<sup>3</sup>, Nodirali S. Normakhamatov<sup>4</sup>, and Ildikó Bácskay<sup>1</sup>

<sup>1</sup>*Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Debrecen, , Rex Ferenc u.1. 4002 Debrecen, Hungary*

<sup>2</sup>*Department of Pharmacology, Faculty of Pharmacy, University of Debrecen, Rex Ferenc u.1. 4002 Debrecen, Hungary*

<sup>3</sup>*MEDITOP Pharmaceutical Ltd., Ady Endre Street 1, 2097 Pilisborosjeno, Hungary*

<sup>4</sup>*Tashkent Pharmaceutical Institute 100015, Toshkent sh, Oybek k, 45, Tashkent, Uzbekistan*

**Introduction:** *Salvia officinalis* is known for its antimicrobial properties, it effectively addresses various skin infections such as acne vulgaris, eczema, and psoriasis by reducing inflammation and infection.

Our experimental work aims to develop modern antioxidant and anti-inflammatory creams targeting the treatment of acne, using medical sage as a natural active ingredient. A key goal is to enhance the solubility and bioavailability of sage extract by incorporating self-nano-emulsifying drug delivery systems (SNEDDS) .

**Method:** We assessed the zeta potential and particle size of the nanoemulsions with the Malvern Zetasizer NanoS instrument, and we tested the pH and texture of various formulations using the CT3 Texture Analyzer. The Franz diffusion method was used to model the release of carnosol. In addition, the biocompatibility of the preparations is mapped using the MTT (2-(4,5-dimethyl-2-thiazolyl)-3,5-diphenyl-2H-tetrazolium bromide) cytotoxicity test examination of its capacity using DPPH (2,2-diphenyl-1-picrylhydrazyl) solution and UV-VIS spectrophotometric measurement. The anti-inflammatory effect was investigated by enzyme-linked immunosorbent assay (ELISA). The in vivo anti-inflammatory effects of the formulations were assessed by measuring rat paw edema.

**Results:** Based on the obtained particle size and zeta potential, it can be established that the SNEDDS formulated with Labrafil M surfactant falls into the nano size range. Tests on the pharmaceutical form have shown that sage preparations containing surfactants (Cremophor and Transcutol HP) have a favourable diffusion profile and do not pose a toxic threat to keratinocytes. DPPH test and enzyme-linked immunosorbent assays (ELISA) showed strong efficacy, with an in vivo carrageenan-induced rat paw edema model revealing that the SNEDDS-based cream significantly reduced inflammation.

**Conclusions:** In the future, sage may be a promising alternative to steroids or antibiotics, or can be used as a supplement to them, as its natural anti-inflammatory and antimicrobial properties can help reduce side effects and support the body's natural defences,

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# THE USE OF HOT-MELT EXTRUSION FOR THE MANUFACTURING OF API CONTAINING FILAMENTS FOR FDM 3D-PRINTING

Bence Vámosi<sup>1</sup>, Petra Arany<sup>1</sup>, Ádám Papp<sup>2</sup>, Dániel Nemes<sup>1</sup>, Pálma Fehér<sup>1</sup>,  
Zoltán Ujhelyi<sup>1</sup>, Prof. Ildikó Bácskay<sup>1</sup>

<sup>1</sup>University of Debrecen, Faculty of Pharmacy, Department of Pharmaceutical Technology,  
Rex Ferenc street 1, H-4002, Debrecen

<sup>2</sup>University of Debrecen, University of Debrecen Clinical Centre, Health Care Service Units,  
University Pharmacy, Pharmacy of Nagyerdei Campus, Nagyerdei körút 98, H-4032, Debrecen

**Introduction:** Hot-melt extrusion (HME) is a widely used technology not only in the pharmaceutical industry but in other levels of industrial manufacturing. A variety of commercially available drugs using this method for example Lacrisert® ophthalmic insert, Zoladex® injectable implant, Implanon® implant, NuvaRing® vaginal ring or Eucras® film-coated tablet. (1) In case of FDM type 3D printing HME is used for the manufacturing of the active pharmaceutical ingredient (API) containing filament for the 3D printing process. Based on a previous review it is crucial to investigate the critical process parameters for a better outcome. (2) The following parameters can be altered: the temperature of the zones, the rotation speed of the screw, the feed rate and the speed of the conveyor belt while the filament is cooling down (3)

**Method:** A systematic review was made about previous publications to see and determine the critical extrusion parameters from a quality by design aspect. Our research group manufacture different API containing filament by hot-melt extrusion. The filaments are characterized by TG/IR, DSC or and texture analysis. The adequate filaments are selected for FDM 3D printing based on a digital design.

**Results:** In the review around 100 articles were analyzed and we can determine that for every composition we have to determine the optimal process parameters and we have to choose wisely the temperature of the zones, the rotation speed of the screw, the feed rate and the speed of the conveyor belt. Even the position of the conveyor belt is effecting the colling process and affects the diameter of the filament. For the better reproducibility “home-fixed” fans needed to be settled.

**Conclusions:** In conclusion, hot-melt extrusion represents an exciting and cutting-edge technology in drug manufacturing and with the adequately chosen parameters it can be easily used for the API containing filament manufacturing as an intermediate product for FDM 3D printing. Over the last two decades, many research groups have worked on to manufacture these filaments to improve the safety, efficacy, and tolerability of medications while providing personalized treatments for patients.

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# BLOOD-BRAIN BARRIER TRANSPORT SYSTEM FOR THERAPY AND DIAGNOSIS OF NEURODEGENERATIVE DISEASES

Kevin James,<sup>1,2</sup> Petra Majerová<sup>2</sup>, Michaela Škrabanová<sup>2</sup>, Ľubica Fialová<sup>2</sup>,  
Krutika Khiratkar<sup>2</sup> and Jozef Hanes<sup>2</sup>

<sup>1</sup>University of Veterinary Medicine and Pharmacy in Košice, Košice, Slovakia

<sup>2</sup>Institute of Neuroimmunology, Slovak Academy of Sciences, Bratislava, Slovakia

**Introduction:** Alzheimer's disease (AD) is characterized by the presence of insoluble aggregates of hyperphosphorylated tau proteins (1,2). While several therapeutic monoclonal antibodies (mAbs) have been approved for clinical use, their efficacy is limited by the blood-brain barrier (BBB), which restricts their passage due to its selective nature (3,4). In this study, we aim to develop a single-chain variable fragment (scFv) with binding affinity to surface receptor proteins of rat endothelial cells, such as low-density lipoprotein receptor-related protein 8 (LRP8) or angulin-1, facilitating receptor-mediated transcytosis (RMT) for improved BBB penetration.

**Methods:** Recombinant LRP8 and angulin-1 proteins were produced using a mammalian cell expression system and used to immunize mice to generate antibodies against these receptors. Monoclonal antibodies were then fragmented to produce scFv. The specificity and efficacy of the antibodies were evaluated using Western blotting, ELISA, immunostainings and flow cytometry. BBB transcytosis of the antibodies was analyzed using an in vitro 2D-BBB model.

**Results:** Currently, we have successfully produced an antibody against the LRP8 receptor and further developed a scFv from it. The LRP8-specific scFv recognizes primary rat endothelial cells and capillaries in rat brain tissue. Permeability experiments demonstrated that the scFv can cross the BBB.

**Conclusion:** Through this study, we aim to develop an efficient drug delivery system capable of crossing the complex BBB, which can also serve as a diagnostic tool for detecting tau pathology. Additionally, we will assess the permeability of the LRP8-specific scFv in a transgenic rat model for tauopathy. Furthermore, we will evaluate the ability of the generated scFv to recognize tau pathology in brain tissue.

**Acknowledgment:** APVV-21-0321, APVV-21-0254, VEGA 2/0075/24, CRP/24/017

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# THE HISTONE DEACETYLASE INHIBITOR SUBEROYLANILIDE HYDROXAMIC ACID PROMOTES BLOOD-BRAIN BARRIER PROTECTION DURING REPERFUSION IN A CELL CULTURE MODEL OF ISCHEMIC STROKE

Zuhao Cui<sup>1,2</sup>, Anikó Szecskó<sup>1,2</sup>, Gergő Porkoláb<sup>1</sup>, Koppány Párdi<sup>1</sup>, László Dér<sup>3</sup>, Krisztina Nagy<sup>3</sup>, Janet Adegbite<sup>1</sup>, Nárcisz Cser<sup>1</sup>, Mária A. Deli<sup>1</sup>, Szilvia Veszélka<sup>1</sup>

*<sup>1</sup>Biological Barriers Research Group, Institute of Biophysics,  
HUN-REN Biological Research Centre, Szeged, Hungary*

*<sup>2</sup>Doctoral School of Biology, University of Szeged, Szeged, Hungary*

*<sup>3</sup>Biophotonics and Biomicrofluidics Research Group, Institute of Biophysics,  
HUN-REN Biological Research Centre, Szeged, Hungary*

**Introduction:** Ischemic stroke is a leading cause of death worldwide with limited available treatment options. During ischemic stroke, reduced blood flow causes severe neuronal damage and BBB disruption. Thrombolytic therapy with recombinant tissue plasminogen activator (rtPA) which acts by breaking down clots to restore blood flow is the only FDA approved treatment for ischemic stroke. However, rtPA is effective within a limited time (4.5 h) of symptom onset with a risk of intracranial hemorrhage. Therefore, additional effective therapeutic approaches for treatment of ischemic stroke are urgently needed. The aim of this study was to investigate the effect of suberoylanilide hydroxamic acid (SAHA), a histone deacetylase inhibitor, on restoring the function of the BBB to prevent post-stroke consequences.

**Method:** We tested the effect of SAHA on a human co-cultured BBB model under normoxia, oxygen-glucose deprivation (OGD), and during reperfusion after OGD (OGD/R).

**Results:** Our results show that after OGD, SAHA is able to prevent the BBB functions by increasing the resistance, and reducing the permeability of marker molecules across the BBB. RNA-seq analyses showed that SAHA decreased the expression of genes involved in inflammatory processes and cell proliferation and increased the expression of glycocalyx related genes. Furthermore, SAHA enhanced the expression of genes of basement membrane components and modulated key pathways by inducing Wnt signaling and inhibiting the NOTCH signaling, which balances vascular growth and branching. After morphological analysis, we also showed that SAHA treatment led to a more elongated and differentiated brain endothelial phenotype.

**Conclusions:** Based on our results, SAHA may be a potential therapeutic tool for the treatment of ischemic stroke, but further research is needed to gain a deeper understanding of its mechanism of action and to develop its potential clinical applicability.

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# DEVELOPMENT OF A MULTIFUNCTIONAL NANOFIBROUS PATCH FOR ORAL APHTAE TREATMENT

Adrienn Kazsoki, Houssam Abboud, Romána Zelkó

*Semmelweis University, University Pharmacy Department of Pharmacy Administration,  
Hőgyes Endre street 7-9, 1094 Budapest, Hungary*

**Introduction:** Oral lichen planus and recurrent aphthous ulcers are painful inflammatory conditions that significantly impact quality of life. Current treatments, such as mouth rinses and gels, offer limited efficacy due to poor adhesion and rapid clearance from the mucosa. Electrospun nanofiber patches present a promising alternative, enabling targeted and prolonged drug delivery.

This research aims to develop a multifunctional nanofiber patch incorporating steroids (anti-inflammatory), hyaluronic acid (tissue regeneration), dexpantenol (wound healing), and lidocaine (pain relief). Additionally, the project aims to comprehensively characterize the morphology and solid-state properties of the developed nanofiber samples.

**Method:** The polyvinyl-alcohol and chitosan-based nanofibrous samples were prepared by electrospinning. The critical precursor solution, process, and formulation parameters were investigated. The electrospun samples were characterized morphologically by scanning electron microscopy, and solid-state characterization was carried out.

**Results:** Adding different molecular weights of PVA improved the electrospinnability of chitosan from a 2 % (V/V) acetic acid solution. Fibrous samples were obtained after adding Mowiol® 18-88 and optimizing the precursor and process parameters of the fiber formation method. FT-IR and XRD measurements indicated that the fiber formation process resulted in amorphous solid dispersions.

**Conclusions:** The developed multifunctional nanofibrous patch can enhance therapeutic outcomes by reducing inflammation and pain while promoting tissue regeneration. Fibrous webs are produced using a continuous, cost-effective, and highly controllable technology that can be integrated into modern pharmaceutical manufacturing.

**Funding:** This project was supported by the EKÖP-2024-181 New National Excellence Program of the Ministry for Culture and Innovation from The Source of the National Research, Development and Innovation Fund.

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# INVESTIGATION OF NEW CANCER TREATMENT STRATEGIES AND SYNTHESIS OF NOVEL NANO-SIZED MATERIALS FOR CANCER TREATMENT

Ahmad Malkawi<sup>1</sup>, Sourav Das<sup>1</sup>, Barack Magwi Nyanswi<sup>2</sup>, Kőszegi Tamás<sup>2,3</sup>, Aleksandar Széchenyi<sup>1</sup>

<sup>1</sup>University of Pécs, Faculty of Pharmacy, Institute for Pharmaceutical Technology and Biopharmacy, Pécs, Hungary

<sup>2</sup>University of Pécs, Medical School, Department of Laboratory Medicine, 7624 Pécs, Hungary

<sup>3</sup>University of Pécs, Molecular Medicine Research Group, Szentágotthai Research Center, 7624 Pécs, Hungary

**Introduction:** Cancer, which is caused by uncontrolled cell proliferation, is a leading cause of mortality globally. Traditional therapies, such as chemotherapy, have downsides, including toxicity and resistance. Ferroptosis, a novel kind of cell death, has shown the potential to destroy cancer cells by accumulating reactive oxygen species. Targeting mechanisms are required to guarantee that cancer cells are eliminated while normal cells are spared. Nanoformulations have the potential to increase therapeutic effectiveness by delivering drugs more precisely.

**Methods:** intracellular iron buildup [1], protein levels [2,3], and antioxidant capability [4] were tested on the Hepg2 cell line, and the MDCK cell line was used to compare iron buildup. A nano-formulation will be created to improve targeted medication distribution, increasing efficacy while lowering toxicity.

**Results:** Preliminary results showed that cancer cells accumulated more iron than normal cells, indicating selective absorption. Artemisinin and erastin promoted ferroptosis in a dose-dependent manner, drastically lowering intracellular protein levels while boosting reactive oxygen species (ROS) generation. While Ferric ammonium citrate increased ROS production in higher concentration

**Conclusion:** This study demonstrates the potential of ferroptosis induction as a novel cancer treatment approach. Optimizing medication combinations and further characterizing nanoformulations for therapeutic applications will be the main goals of future research.

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# INVESTIGATION OF A PENTAPEPTIDE CARRIER ON CULTURE MODELS OF THE BLOOD-BRAIN AND EPITHELIAL BARRIERS

Ilona Gróf<sup>\*1</sup>, Alexandra Bocsik<sup>1</sup>, Enikő Szabó<sup>2</sup>, Imre Norbert<sup>3</sup>, Tamás Martinek<sup>3</sup> and Mária A. Deli<sup>1</sup>

<sup>1</sup>*Institute of Biophysics, HUN-REN Biological Research Centre, Szeged, Hungary*

<sup>2</sup>*Institute of Genetics, HUN-REN Biological Research Centre, Szeged, Hungary*

<sup>3</sup>*Department of Medical Chemistry University of Szeged, Szeged, Hungary*

**Introduction:** Biological barriers make the treatment of many diseases difficult, as they block the delivery of biopharmaceutics at therapeutically relevant concentrations. Therefore, targeted delivery of protein drugs to the intracellular space and through biological barriers is an actively investigated area. One of the promising candidates are the glycan-recognizing peptides. Our research group has previously shown that the galectin-1- derived WYKYW pentapeptide binds to GM1 ganglioside on the cell surface at nanomolar concentrations and is capable of delivering large proteins into the intracellular space via lipid-raft mediated/ caveolar endocytosis without being trapped in lysosomes (Imre et al., 2020). The WYKYW peptide is small and does not influence the viability of cells, thus it is a promising candidate as a carrier for proteins to cross biological barriers. Since no data are available on whether WYKYW is suitable for delivering large proteins into cells or for transfer through cell layers, our aim was to compare the cellular entry of the peptide complexes into cells and their penetration across culture models of the blood-brain and different epithelial barriers.

**Method:** Human brain endothelial cells and human epithelial cells (alveolar, corneal, intestinal) were cultured on glass bottom dishes to investigate the intracellular localization of the WYKYW-protein complex by confocal microscopy. For the transcytosis experiment epithelial cells were cultured as monoculture and endothelial cells were co-cultured on cell culture inserts with brain pericytes. After the permeability experiment the immunostaining of intercellular junction proteins was performed.

**Results:** We observed that the peptide-protein complex entered both epithelial and endothelial cells and localized in the cytoplasm. Image analysis showed that the highest amount of complex entered into the alveolar epithelial cells followed by the cornea-, intestinal epithelium and the brain endothelial cells. We have shown that there was no difference in the penetration of the peptide-protein complex and the protein alone through the cell layers. The peptide treatment did not change the staining pattern of intercellular junctions of either epithelial or endothelial cells, showing that the tightness of the barriers was not compromised.

**Conclusions:** Our results suggest that the WYKYW pentapeptide is suitable for delivering large proteins into cells through a specific endocytotic pathway, but does not enhance the transcellular passage of proteins.

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# MORPHOLOGICAL AND FUNCTIONAL CHARACTERIZATION OF A NEW HUMAN STEM CELL BASED BLOOD-BRAIN BARRIER AND BRAIN ORGANOID LAB-ON-A-CHIP MODEL

Judit P. Vigh,<sup>1,2</sup> Anna E. Kocsis<sup>1</sup>, Ana R. Santa-Maria<sup>1,3</sup>, Nóra Kucsápszky<sup>1</sup>,  
Silvia Bolognin<sup>4</sup>, Jens C. Schwamborn<sup>4</sup>, András Kincses<sup>1</sup>, Gergő Porkoláb<sup>1,5</sup>,  
Anikó Szecskó<sup>1,2</sup>, Mária Mészáros<sup>1</sup>, Roland Wirth<sup>6</sup>, Szilvia Veszélka<sup>1</sup>, András Dér<sup>1</sup>,  
Mária A. Deli<sup>1</sup>, Fruzsina R. Walter<sup>1</sup>

<sup>1</sup>*Institute of Biophysics, HUN-REN Biological Research Centre, Temesvári krt.62., 6726 Szeged, Hungary;* <sup>2</sup>*Doctoral School of Biology, University of Szeged, Dugonics tér 13., 6720 Szeged, Hungary;* <sup>3</sup>*Wyss Institute for Biologically Inspired Engineering at Harvard University, 201 Brookline Ave, Boston, MA 02215, USA;* <sup>4</sup>*Luxembourg Centre for Systems Biomedicine, University of Luxembourg, 7 Av. des Hauts-Fourneaux, 4362 Belvaux, Luxembourg;* <sup>5</sup>*Smurfit Institute of Genetics, Trinity College Dublin, College Green, Dublin 2, Ireland;* <sup>6</sup>*Institute of Plant Biology, HUN-REN Biological Research Centre, Temesvári krt.62., 6726 Szeged, Hungary*

**Introduction:** The blood-brain barrier (BBB) protects the brain and provides oxygen and nutrients for the central nervous system (CNS), but it also restricts the entry of pharmaceutical drugs into the brain. Cell culture models became essential to investigate cerebral drug delivery. Microfluidic chip devices allow complex and physiological modelling of the BBB. Induced pluripotent stem cell (iPSC) based technologies, the formation and use of human brain organoids provide simplified 3D modeling. Our aim was to (1) create and optimize a new, dynamic cell culture lab-on-a-chip model by the co-culture of a BBB model and human midbrain organoids, and to (2) examine BBB properties and functionality in the presence of organoids.

**Method:** Human stem cell derived endothelial cells and brain pericytes were used to establish the BBB model (Cecchelli et al., 2014). Human midbrain organoids were differentiated from healthy donor iPSCs (Nickels et al., 2020). The barrier integrity of the BBB model was investigated in the presence of midbrain organoids in a dynamic setup by the measurement of impedance and permeability for fluorescent markers. 4.4 kDa FITC-dextran as paracellular and 67 kDa Evans blue-labeled albumin as a transcellular marker were used. The morphology of brain endothelial cells was examined by immunocytochemistry for tight junction proteins. Functionality of the model was tested by the passage of nanocarriers across the BBB and by characterizing the uptake into the organoids. We examined the indirect effect of clinically used contrast agent Iopamidol on brain organoids.

**Results:** Our results indicate that the BBB integrity was appropriate in the presence of midbrain organoids. We characterized the midbrain organoids which were co-cultured with the BBB by immunohistochemistry for MAP2,  $\beta$ III-tubulin and GFAP. We found that nanoparticles crossed through the BBB and entered the organoids effectively. Iopamidol opened the blood-brain barrier and damaged the neuronal network within the organoids.

**Conclusions:** This complex organ-on-a-chip system can be a valuable tool for further experiments in toxicological, pharmacological and pathology testing.

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# STUDY OF VARIOUS NAIL LACQUER FORMING TRANSUNGUAL DRUG DELIVERY SYSTEMS

Zsófia Kohod<sup>1</sup>, Noémi Anna Niczinger<sup>1</sup>, Nikolett Kállai-Szabó<sup>1</sup>,  
Richárd Levente Kozma<sup>1</sup>, István Antal<sup>1</sup>

<sup>1</sup>*Semmelweis University, Faculty of Pharmaceutical Sciences, Department of Pharmaceutics,  
Hőgyes Endre u. 7., 1092 Budapest, Hungary*

**Introduction:** Drug delivery through human nails, known as transungual drug delivery systems, is becoming a trend in the pharmaceutical field. They are essential for the treatment of many nail diseases (e.g.: Onychomycosis, Onycholysis, Psoriasis, etc.). This application method has the potential to reduce the occurrence of adverse effects by circumventing first-pass metabolism. The aim of our study was to investigate the physical properties of pharmaceutical nail lacquers available on the market.

**Method:** Evaluation of marketed film formulation was observed through physical properties such as, drying rate, tensile strength, viscosity. The resistance of films formed on artificial nails was investigated under in vitro conditions, in various liquid media, for different periods of time.

**Results:** The drying rate of the various preparations was found to be adequate to ensure patient compliance. The tensile strength and viscosity highly influence the cover ratio of the complete nail surface. The viscoelastic properties of Newtonian fluids, such as nail lacquers, enable them to be applied to the nail plate with ease. According to the results, the resistance of the nail lacquers was higher in natural waters in comparison to for e.g.: chlorinated water.

**Conclusions:** Our investigations were based on the preparations available on the market, showing the importance of transungual drug delivery systems in the treatment of nail disorders. The successful pharmaceutical treatment of nail diseases requires appropriate and homogenous dose in the formulation as well as, after the film formulation. The comparison of the pharmaceutical nail lacquers was examined in accordance with application: viscosity, texture, drying rate, film- forming.

# DEVELOPMENT OF CLOTRIMAZOL-CONTAINING EMULGELS FOR THE TREATMENT OF VAGINAL CANDIDIASIS: IN VITRO STUDIES

Zsófia Vilimi, Zsófia Kohod, Richárd Levente Kozma, Zsófia Szabó, Lilla Dorottya Kóró,  
Krisztina Ludányi, Nikolett Kállai-Szabó, István Antal

*Semmelweis University, Department of Pharmaceutics, Hőgyes E. u. 7-9,  
1092, Budapest, Hungary*

**Introduction:** Recurrent vulvovaginal candidiasis affects an estimated 138 million individuals worldwide each year, significantly impacting their quality of life [1]. While numerous treatment options are available, many are associated with unpleasant side effects [2]. Our research aimed to develop a clotrimazole containing emulgel that minimizes the discomfort commonly experienced with vaginal drug formulations, making it more user-friendly. Additionally, we aimed to create a drug delivery system capable of providing prolonged and sustained release of the active ingredient, ensuring a continuous therapeutic effect lasting throughout the night.

**Method:** For the preparation of emulgels, we used hydrogels containing different types of poloxamers in different ratios as a base. To enhance mucoadhesivity, hydroxypropyl methylcellulose (HPMC) was added to the hydrogels in varying concentrations. Oleic acid was used as the oil phase of the emulgels, in which the therapeutic amount of clotrimazole was pre-dissolved. The formulated gels were subjected to rheological analysis, stability testing, mucoadhesivity measurements and spreadability assessment. Their drug release properties were examined using two methods: by using vertical diffusion cells and a paddle dissolution apparatus. The amount of released active ingredient was determined by HPLC in the first case and by spectrophotometer in the second [3].

**Results:** By adjusting the ratios of poloxamer and HPMC, we were able to create gels with varying stability. Increasing the HPMC content improved mucoadhesiveness but did not always favor the integrity of the gel structure. Changes in stability were confirmed not only by rheological measurements but also by spreadability tests. Both in vitro drug release methods demonstrated sustained drug release, which could also be modulated by altering the ratios of HPMC and poloxamers.

**Conclusions:** The developed clotrimazole-containing emulgels offer a promising therapeutic option for the treatment of vaginal candidiasis. The combination of a mucoadhesive, oil-based formulation with thermoresponsive hydrogels enables sustained drug release and can improve patient compliance. Oleic acid plays a dual role: it enhances clotrimazole solubility while also supporting the health of the vaginal microbiom. By optimizing the ratio of poloxamer and HPMC, we successfully formulated a product with appropriate rheological properties, ease of application, and prolonged drug release. Further in vivo studies are needed to validate the clinical efficacy and safety of the formulation, but based on current results, this novel emulgel represents a significant advancement in the treatment of vaginal candidiasis.

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# MODULATION OF MULTISPECIFIC TRANSPORTERS BY UNCARIA TOMENTOSA EXTRACT AND ITS MAJOR PHYTOCONSTITUENTS

Nóra Szilvász<sup>1</sup>, Judit Hohmann<sup>2,3</sup>, István Zupkó<sup>4</sup>, Zsuzsanna Gáborik<sup>1</sup>,  
Csilla Temesszentandrás-Ambrus<sup>1</sup>

<sup>1</sup>Charles River Laboratories Hungary, H-1117 Budapest, Hungary

<sup>2</sup>Institute of Pharmacognosy, University of Szeged, Eötvös Street 6, 6720 Szeged, Hungary

<sup>3</sup>ELKH-USZ Biologically Active Natural Products Research Group, University of Szeged,  
6720 Szeged, Hungary

<sup>4</sup>Institute of Pharmacodynamics and Biopharmacy, University of Szeged, Eötvös Street 6,  
6720 Szeged, Hungary

**Introduction:** Uncaria tomentosa (UT), a traditionally used herb is attributed to several health benefits including anti-inflammatory, immunomodulatory and anticancer effects (1,2). However, to date neither the U.S. Food and Drug Administration (FDA) nor the European Medicines Agency (EMA) approved it for medicinal use resulting in that potential herb-drug interactions (HDIs) are not requested to be investigated prior to commercialization (3). The most common mechanism leading to HDIs is the inhibition and/or induction of transport proteins and drug-metabolizing enzymes by herbal ingredients, causing changes in the pharmacokinetic disposition of the victim drug (4). The present study aimed to determine the potential transporter mediated interactions of UT.

**Method:** The effect of UT extract and its 3 major oxindole alkaloid components were investigated on 25 solute carrier (SLC) and 8 ATP-binding cassette (ABC) transporters using validated transporter overexpressing cell-based assays, and transporter overexpressing cell membrane derived vesicle assays.

**Results:** UT extract significantly inhibited all ABC transporters and the majority of the SLC transporters tested. Of the investigated oxindole alkaloids, isopteropodine significantly inhibited OATP, OCT1 and OCT2, OAT3, ENT4, MDR1, and BCRP transporters. OCTs, OCTN1-, ENT1-, and MDR1-mediated substrate accumulation was below 50% in the presence of mitraphylline, while Uncarine D inhibited OCT1 mediated uptake by 50%.

**Conclusions:** Based on the calculated intestinal concentration of UT extract, interactions with intestinal transporters that are directly exposed to the UT product especially OATP2B1, ENTs, MRP1, MRP2, MDR1, and BCRP could be relevant in vivo. Our results could help to predict the potential clinical consequences of UT co-administration with drugs, such as increased toxicity or altered efficacy. In conclusion, the use of these in vitro models is applicable for the analysis of transporter-mediated HDIs similar to drug–drug interaction (DDI) prediction.

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## CONFERENCE PARTICIPANTS

| First name | Last name            | Position                                                                      | Institution                                                                                              | Country  |
|------------|----------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------|
| Houssam    | ABBOUD               | PhD Student                                                                   | Semmelweis University                                                                                    | Hungary  |
| Rita       | AMBRUS               | Full Professor                                                                | University of Szeged Institute of Pharmaceutical Technology and Regulatory Affairs                       | Hungary  |
| Istvan     | ANTAL                | Full Professor, Dean                                                          | Semmelweis University - Department of Pharmaceutics                                                      | Hungary  |
| Petra      | ARANY                | Assistant Professor                                                           | University Of Debrecen, Faculty of Pharmacy, Department of Pharmaceutical Technology                     | Hungary  |
| Rania      | AWAD                 | Ph.D Candidate                                                                | Technion the Israel Institute of Technology                                                              | Isreal   |
| Ildikó     | BÁCSKAY<br>PROF. DR. | Full Professor, Dean                                                          | University Of Debrecen, Faculty of Pharmacy, Department of Pharmaceutical Technology                     | Hungary  |
| Diana      | BALOGH-WEISER        | Assistant Professor                                                           | Budapest University of Technology and Economics                                                          | Hungary  |
| Heba       | BANAT                | PhD Candidate                                                                 | University of Szeged, Faculty of Pharmacy, Institute of Pharmaceutical Technology and Regulatory Affairs | Hungary  |
| Bálint     | BASA                 | Resident                                                                      | Semmelweis University - Department of Pharmaceutics                                                      | Hungary  |
| Tímea      | BESKID               | Student                                                                       | Pázmány ITK, Budapest                                                                                    | Hungary  |
| Mangesh    | BHIDE                | Professor, Head of the Laboratories of Biomedical Microbiology and Immunology | University of Veterinary Medicine and Pharmacy in Kosice                                                 | Slovakia |
| Thomas     | BIRNGRUBER           | Head of Research Group, Deputy Head of Institute                              | Health                                                                                                   | Austria  |
| Benedek    | BIRO                 | Student                                                                       | Pázmány ITK, Budapest                                                                                    | Hungary  |
| Zuhao      | CUI                  | PhD Student                                                                   | HUN-REN Biological Research Centre, Szeged                                                               | Hungary  |
| Máté       | CSANAKI              | Student                                                                       | Pázmány ITK, Budapest                                                                                    | Hungary  |
| ILDIKO     | CSÓKA<br>PROF. Dr.   | Head of Institute, Professor                                                  | Pharmaceutical Technology and Regulatory Affairs                                                         | Szeged   |
| Mária      | DELI                 | Institute Director, Research Professor                                        | HUN-REN Biological Research Centre                                                                       | Hungary  |
| Ferenc     | ENDER                | CEO                                                                           | Spinsplit LLC                                                                                            | Hungary  |
| Franciska  | ERDŐ                 | Full Professor                                                                | Pázmány ITK, Budapest                                                                                    | Hungary  |
| Amir       | FAHMI                | Full Professor                                                                | Rhein-Waal University of Applied Sciences                                                                | Germany  |
| Pálma      | FEHÉR DR.            | Associate Professor                                                           | University Of Debrecen, Faculty of Pharmacy, Department of Pharmaceutical Technology                     | Hungary  |

| First name               | Last name          | Position                                      | Institution                                                                               | Country     |
|--------------------------|--------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------|-------------|
| Lívia                    | GÁL                | RA Director                                   | MEDITOP Pharmaceutical Ltd.                                                               | Hungary     |
| Anja                     | GOLEMAC<br>LIPOVAC | Research Engineer                             | University of Split; Mediterranean<br>Institute for Life Sciences (MedILS)                | Croatia     |
| Ilona                    | GRÓF               | Research Associate                            | HUN-REN Biological Research Centre,<br>Szeged                                             | Hungary     |
| Miklós                   | GYÖNGY             | Associate Professor                           | Pázmány ITK, Budapest                                                                     | Hungary     |
| Balazs                   | HALLGAS            | CEO                                           | Navolab Diagnostics Ltd.                                                                  | Hungary     |
| Patrik<br>Márton         | HANTOS             | Student                                       | Pázmány ITK, Budapest                                                                     | Hungary     |
| Daniel                   | HILLIER            | Assistant Professor                           | Pázmány ITK, Budapest                                                                     | Hungary     |
| Kevin                    | JAMES              | PhD Student                                   | Institute of Neuroimmunology,<br>Slovak academy of sciences,<br>Bratislava                | SLovakia    |
| Éles                     | JÁNOS              | Head of Medicinal Che-<br>mistry              | Gedeon Richter Plc.                                                                       | Hungary     |
| Karoly                   | KANAI              | Hon. Assoc. Prof                              | Budapest University of Technology<br>and Economics                                        | Hungary     |
| Miroslav                 | KANDAR             | Sales and Marketing<br>Manager                | MatTek In Vitro Life Science<br>Laboratories                                              | Slovakia    |
| Gábor                    | KATONA             | Associate Professor                           | University of Szeged, Institute of<br>Pharmaceutical Technology and<br>Regulatory Affairs | Hungary     |
| Dorottya                 | KOCSIS             | PhD Candidate                                 | Pázmány ITK, Budapest                                                                     | Hungary     |
| Zsófia                   | KOHOD              | Resident                                      | Semmelweis University- Department<br>of Pharmaceutics                                     | Hungary     |
| Mátyás                   | KOVÁCS             | Study Director                                | CRL Hungary Kft.                                                                          | Hungary     |
| Nóra                     | KRAJCS DR.         | Study Director                                | CRL Hungary Kft.                                                                          | Hungary     |
| András                   | LAKI               | Associate Professor                           | Pázmány ITK, Budapest                                                                     | Hungary     |
| Miléna                   | LENGYEL            | Senior Lecturer                               | Semmelweis University                                                                     | Hungary     |
| Balázs                   | LIGETI             | Associate Professor                           | Pázmány ITK, Budapest                                                                     | Hungary     |
| Eszter                   | LOMEN              | QMS Manager                                   | Navolab Diagnosztika Kft.                                                                 | Hungary     |
| Kende                    | LŐRINCZ            | Assistant Professor                           | Semmelweis University- Department<br>of Dermatology                                       | Hungary     |
| Petra                    | MAJEROVA           | Research Scientist                            | Institute of Neuroimmunology, SAS,<br>Bratislava, Slovakia                                | Slovakia    |
| Ahmad<br>Sameer<br>Yahia | MALKAWI            | PhD Student                                   | Institute of Pharmaceutical<br>Technology and Biopharmacy, Pecs<br>University             | Hungary     |
| Ferenc                   | MARKOS DR.         | Development Pharmaceu-<br>tical Technologist  | MEDITOP Pharmaceutical Ltd.                                                               | Hungary     |
| Tshepang                 | MQATYWA            | MSc Student                                   | Pázmány ITK, Budapest                                                                     | Hungary     |
| Stefan                   | MÜHLEBACH          | External Member in Re-<br>search and Teaching | University of Basel, Dept.<br>Pharmaceutical Sciences                                     | Switzerland |

| First name          | Last name             | Position                          | Institution                                                                                    | Country  |
|---------------------|-----------------------|-----------------------------------|------------------------------------------------------------------------------------------------|----------|
| <b>Fruzsina</b>     | <b>NACSA DR.</b>      | Head of Pharmaceutical Laboratory | MEDITOP Pharmaceutical Ltd.                                                                    | Hungary  |
| <b>Winfried</b>     | <b>NEUHAUS</b>        | Principal Scientist               | AIT Austrian Institute of Technology GmbH & Danube Private University (DPU) Krems              | Austria  |
| <b>Adrienn</b>      | <b>NOCHTA-KAZSOKI</b> | Assistant Professor               | Semmelweis University                                                                          | Hungary  |
| <b>Marek</b>        | <b>PUSKAR</b>         | Junior Scientist                  | MatTek In Vitro Life Science Laboratories                                                      | Slovakia |
| <b>Emily</b>        | <b>REIS</b>           | Production Manager                | MatTek In Vitro Life Science Laboratories                                                      | Slovakia |
| <b>Marina</b>       | <b>RUDAN DIMLIĆ</b>   | Research Associate                | University of Split; Mediterranean Institute for Life Sciences (MedILS)                        | Croatia  |
| <b>Ágnes</b>        | <b>RUSZNYÁK DR.</b>   | Assistant Professor               | University of Debrecen, Department of Molecular and Nanopharmaceutics, Faculty of Pharmacy     | Hungary  |
| <b>Norman</b>       | <b>SEPSIK</b>         | Student                           | Budapest University of Technology and Economics                                                | Hungary  |
| <b>Bence</b>        | <b>SIPOS</b>          | Assistant Professor               | University of Szeged, Institute of Pharmaceutical Technology and Regulatory Affairs            | Hungary  |
| <b>Gábor</b>        | <b>STEFÁN</b>         | Sales Manager                     | ABL&E-JASCO Hungary Ltd.                                                                       | Hungary  |
| <b>Boglárka</b>     | <b>SZALAI</b>         | PhD Student                       | University of Szeged                                                                           | Hungary  |
| <b>Aleksandar</b>   | <b>SZÉCHENYI</b>      | Senior Scientific Associate       | University of Pécs, Faculty of Pharmacy Institute of Pharmaceutical Technology and Biopharmacy | Hungary  |
| <b>Anikó</b>        | <b>SZECSKÓ</b>        | PhD Student                       | HUN-REN Biological Research Centre                                                             | Hungary  |
| <b>Gábor</b>        | <b>SZEDERKÉNYI</b>    | Full Professor                    | Pázmány ITK, Budapest                                                                          | Hungary  |
| <b>Ildikó</b>       | <b>SZEPESI</b>        | General Manager                   | ABL&E-JASCO Hungary Ltd.                                                                       | Hungary  |
| <b>Fanni</b>        | <b>SZEPETNEKI</b>     | Student                           | Pázmány ITK, Budapest                                                                          | Hungary  |
| <b>Nóra</b>         | <b>SZILVÁSY</b>       | Research Scientist                | Charles River Laboratories Hungary                                                             | Hungary  |
| <b>Péter</b>        | <b>TÁTRAI</b>         | Senior Scientist                  | Charles River Laboratories Hungary                                                             | Hungary  |
| <b>Gergő Dániel</b> | <b>TÓTH</b>           | Application Engineer              | SpinSplit LLC                                                                                  | Hungary  |
| <b>Miklós</b>       | <b>VECSERNYÉS</b>     | Full professor, Former-Dean       | University Of Debrecen, Faculty of Pharmacy, Department of Pharmaceutical Technology           | Hungary  |
| <b>Judit P.</b>     | <b>VIGH</b>           | PhD Student                       | Institute of Biophysics, HUN-REN Biological Research Centre, Szeged                            | Hungary  |
| <b>Zsófia</b>       | <b>VILIMI</b>         | PhD Student/Resident              | Semmelweis University- Department of Pharmaceutics                                             | Hungary  |
| <b>Fruzsina</b>     | <b>WALTER</b>         | Senior Research Associate         | HUN-REN Biological Research Centre, Szeged                                                     | Hungary  |
| <b>Romána</b>       | <b>ZELKÓ</b>          | Full professor, Former-Dean       | Semmelweis University                                                                          | Hungary  |

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Pázmány Péter Catholic University  
**Faculty of Information Technology and Bionics**

H-1083 Budapest, Práter u. 50/a.  
<https://itk.ppke.hu/en>

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