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Contents

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Acta Pharmaceutica Hungarica – 7th BBBB Edition – Greeting 87. 87 2017.

Greetings

It is a pleasure of the Hungarian Society for Pharmaceutical Sciences that the 7th BBBB Conference is held in Hungary, where this conference series started in 2005. The goal of the founders by organizing regional conferences named **"The Balaton-Baltic-Bled-Bosphorus Conference on Pharmaceutical Sciences"** was to establish a close cooperation among the Pharmaceutical Societies of Hungary, Finland, Estonia, Slovenia and the Turkish Pharmaceutical Technology Scientists' Association, member organizations of EUFEPS.

This scientific forum traditionally gathers the members of these Societies and colleagues from neighboring and other countries, and serves as a strong and stable background for permanent dialogue between pharmacists and professionals working in the fields of pharmaceutical sciences, drug research and development.

The conference provides the possibility for the participants to present new results, discuss recent developments and future directions of the pharmaceutical sciences in a broad sense. It offers a good opportunity to promote scientific achievements for talented young pharmacists in Pharmaceutical Companies, Departments of Pharmaceutical Faculties and Academic Institutes. Other goals of this regional conference series include the initiation of common research projects, and fostering the application of the results of new approaches for the accelerated development and introduction of safer and more effective medicines.

I am pleased that more than 400 colleagues will participate at the conference. We have received 280 abstract submissions, and the program includes 11 plenary lectures, 67 oral and 188 poster presentations.

I am looking forward to having a successful conference at Balatonfüred with vivid and fruitful discussions.

Prof. Éva Szökő
Chair of the 7th BBBB International Conference on Pharmaceutical Science

Acta Pharmaceutica Hungarica – 7th BBBB Edition – Committees 87. 88-89 2017.

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Acta Pharmaceutica Hungarica – 7th BBBB Edition – Curriculum Vitae 87. 90-97 2017.

Curriculum Vitae of Invited Speakers

Erem Bilensoy

Department of Pharmaceutical Technology, Hacettepe University, Faculty of Pharmacy, Ankara, Turkey

Erem Bilensoy is full professor of pharmaceutical technology. She graduated from Hacettepe University Faculty of Pharmacy in 1992. She obtained her double Ph.D. degree with a co-tutelle thesis between Université Paris-Sud and Hacettepe University in 2002 under the supervisions of Dominique Duchene and Atilla Hıncal on the *evaluation of amphiphilic* ß-cyclodextrins *modified on the primary face as novel excipients in the preparation of nanospheres and nanocapsules*. She has been appointed as associate professor in 2007 and received full professor position in 2013. She is the author of more than 60 scientific articles, 11 international book chapters receiving more than 1100 citations with a current H-index of 21. She also worked as Editor of the book entitled "Cyclodextrins in the Field of Pharmaceutics, Cosmetics and Biomedicine: Current and Future Industrial Applications" published by John Wiley&Sons in 2012. Dr. Bilensoy served as Bioavailability/Bioequivalence Evaluation Commission member within Turkish Medicines and Medical Devices Agency between 2007-2012 and from December 2015 onwards. She was Vice Dean of Faculty of Pharmacy between 2010-2013. She is founder member and Head for EUFEPS Network on Nanomedicine and Board Member for European Cyclodextrin Society. Erem Bilensoy joined European Federation for Pharmaceutical Sciences EUFEPS Executive Committee in 2012 and was elected as President of EUFEPS starting from June 2015. She is also on the Consultancy Board for Projects on Nanobiotechnology at TUBİTAK Turkish Scientific and Technological Research Council. She was recently elected as Vice Chairman for Hacettepe Technology Transfer Center Executive Committee on January 2016. Her current research interests include targeted nanoparticles in cancer therapy, cationic nanoparticles, cyclodextrin-based drug delivery, inkjet and 3D printed drug delivery systems, biomedical applications of nanoparticles and regulatory approaches on bioavailability/bioequivalence.

Erik Bogsch Jr.

Head of the Biotechnology R&D Division at Gedeon Richter Plc.

Dr. Erik Bogsch is Head of the Biotechnology R&D Division at Gedeon Richter Plc. He is responsible for leading the R&D effort in the development of GR's biotechnology pipeline. Gedeon Richter Plc. is engaged in the development and manufacture of both bacterial cell fermentation based and mammalian cell fermentation based biosimilar products. GR has R&D, analytical & manufacturing capabilities in multiple locations in Hungary & Germany. Dr. Bogsch, has a Natural Sciences degree from the University of Cambridge and a PhD in cell biology from the University of Warwick. Following a brief postdoctoral academic research career, he worked in the food industry for many years in R&D, Quality & Manufacturing roles in the UK, Hungary & Germany. He joined Gedeon Richter Plc. in 2012, as commissioning lead for GR's biotechnology factory in Debrecen, Hungary, before moving into his current role in 2014.

Gustav Boije af Gennäs

University of Helsinki, Finland

Dr. Gustav Boije af Gennäs is a Principal Investigator of the Drug Discovery Group at the Faculty of Pharmacy, University of Helsinki. His main research interests include regenerative medicine, inhibitors of pathogenic parasites, cancer, therapy of Alzheimer's and Parkinson's diseases and the development of microchip technology. Dr. Boije af Gennäs has published over 20 peer-reviewed scientific articles, two patents, and supervised 5 PhD and 18 MSc students. Currently he leads a group of 4 PhD and 2 MSc students in the Synthetic Medicinal Chemistry group that uses state-of-the-art methods in the design and synthesis of novel drug-like compounds, such as stem cell inducers as well as kinase and other enzyme inhibitors and activators. In addition, he develops microchips for novel applications such as bioanalysis and organic reaction analysis. Dr. Boije af Gennäs has been the head of several research projects including those funded by the Academy of Finland and the University of Helsinki, and is involved in projects funded by the Finnish Funding Agency for Technology and Innovation (TEKES), EU, Jane and Aatos Erkko Foundation etc. He has had several invited plenary and keynote presentations in international and national scientific conferences. Dr. Boije af Gennäs is a board member in international scientific committees, evaluation panels and societies. In 2012 he was granted the highly distinguished Academy of Finland postdoctoral project that was continued by the Key Project Funding in 2016. In addition, he received the University of Helsinki Three-year-grant in 2016 and obtained the Finnish Society of Sciences and Letters Award by the Ruth and Nils-Erik Stenbäck Foundation as well as the Young Researcher Award by the University of Helsinki, both in 2016.

István Greiner

Research Director, Gedeon Richter Plc.,

István Greiner graduated at Technical University of Budapest in 1984 as chemical engineer (M.Sc.). He works at Gedeon Richter Plc. since there, at the beginning as research scientist. He got his Ph.D. at Institute of Organic Chemistry of the same university. In 1992 he was appointed as Deputy Head of Chemical and Biotechnological Research and Development. He got his MBA degree at Open University in 1997. He is a patent attorney too, and from 1996 he also headed the Intellectual Property Department at Gedeon Richter Plc. for two and a half year. In 1998 he was appointed to the Director of Chemical and Biotechnological Research and Development, and from 2001 he works for the company as the Deputy of the Research Director too. His responsibility was all the API (Active Pharmaceutical Ingredients) research and development activities including new chemical entity, generic and biotechnological projects. He directed chemical R&D during discovery and development of the FDA approved cariprazine. From 1st of August 2014 he was promoted to Research Director of the Company. He is inventor of seven patents, invited as plenary speaker for international and domestic conferences and has more than 90 publications in well known peer reviewed international journals.

Mojca Kerec-Kos

University of Ljubljana, Slovenia

Since 1999 she has been working at the Chair of Biopharmacy and pharmacokinetics. Her recent scientific work is focused on drugs pharmacokinetics in special population, such as elderly and children, with the aim to optimise the safety and efficacy of pharmacotherapy. She is also actively involved in research activities in the area of clinical pharmacy. Her other research focus is on bioadhesive polymers, which increase the permeability of urinary bladder epithelia and enhance drug permeation into the bladder wall or by desquamation of superficial urothelial cells provide a promising treatment of bacterial cystitis and superficial bladder cancer.

Müge Kilicarslan

Ankara University, Faculty of Pharmacy, Department of Pharmacutical Technology, 06100 Tandoğan, Ankara, Turkey

Muge Kilicarslan is Associate Professor of Pharmaceutical Technology at Ankara University, Faculty of Pharmacy, Turkey. She is graduated from Ankara University Faculty of Pharmacy in 1990. She received her M.Sc. degree on Pharmaceutical Technology with her thesis on the formulation of some drugs conserve in plastic syringes in the same university. She obtained her Ph.D. degree in 1999 on the preparation of multiparticulate oral controlled release dosage form of verapamil HCl. She studied on the in situ implants at College of Pharmacy, Institute of Pharmaceutical Technology, Freie Universitat, Berlin for post-doctoral research. Dr. Kilicarslan worked as Assistant Professor from 2010 to 2015 and received her Associate Professor title in 2015 at the same faculty and department. She studied at several research projects as assistant researcher and research manager. She is currently continuing her research work at the same department. Her current research interest revolves around micro and nanoparticulate drug delivery systems, micromeritics, dental and periodontal drug delivery systems and in situ implants. Her interests also include Good Manufacturing Practices, Quality Assurance and Quality by Design. She is writer of a national book chapter and one of the writers of national book. She has more than twenty papers in the international and national journals and has given several poster presentations and invited lectures. She is also serving as Vice Dean of Faculty of Pharmacy at Ankara University since June 2016.

Petra Kocbek

Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

Petra Kocbek is Associate Professor in Pharmaceutical Nanotechnology at University of Ljubljana, Faculty of Pharmacy. She received her Ph.D. in Pharmaceutical Sciences in 2008. Her main research interests include nanomaterials for the delivery of small molecular weight drugs as well as biomacromolecules. Her recent scientific work is focused on the drug-loaded electrospun polymer nanofibers for application in oral cavity and on the magnetically responsive nanocarriers based on superparamagnetic iron oxide nanoparticles for the targeted cancer therapy. The results of her research have been presented at numerous scientific meetings and have been published in more than 20 peer-reviewed articles that have already received over 800 pure citations. P. Kocbek received Krka Prize for special research achievements in 2008 and Jožef Stefan Golden Emblem award for outstanding contributions made to science in the doctoral thesis in 2011.

Karin Kogermann

Institute of Pharmacy, University of Tartu, Nooruse 1, 50411 Tartu, Estonia

Dr. K. Kogermann is a pharmacist specialized in pharmaceutical technology and physical pharmacy. She received her master degree at the University of Tartu (UT). She completed her PhD at the University of Helsinki, Finland in 2008 entitled: „Understanding solid-state transformations during dehydration: new insights using vibrational spectroscopy and multivariate modeling". After the defense she continued her scientific career at the UT. In 2012 she received a Mobilitas Postdoctoral Research Fellow grant and continued her studies in the field of biotechnology at the Institute of Technology, Antibiotics Laboratory (UT). The main aim of her postdoctoral research was to develop *in vitro* and *in vivo* infection models in mice and understand the action mechanisms of antibiotics. Currently she is working as an Associate Professor and senior researcher at the Institute of Pharmacy.

K. Kogermann has been acting as a grant holder/principal investigator in several Estonian Science Foundation Projects. Her research interests include the physical pharmacy and solid state analysis-related as well as infection and antibacterial therapy-related topics. Her present research is focused on combining these two branches and develop antimicrobial nanofibrous dressings as controlled drug delivery systems for effective wound care and investigation of their performance. The main goal is to understand the effects of the solid-state, mechanical and technological properties on the bioactivity of wound dressings. Hence the drug release, antimicrobial activity, and biofilm formation studies are the main part of the study.

She has (co-)authored 24 original peer-reviews research publications and more than 100 conference proceedings. She has supervised 3 PhD students and currently is supervising 5 PhD students. K. Kogermann is acting as an expert at the European Pharmacopoeia Commission Expert Group G12, Estonian State Agency of Medicine and is a chairman of the Estonian Academical Society.

András Kotschy

Servier Research Institute of Medicinal Chemistry

András Kotschy is the managing director of the Servier Research Institute of Medicinal Chemistry in Budapest, Hungary. After completing his PhD degree in 1995 he joined the staff of Eötvös Loránd University where he rose through the ranks to associate professor also completing his habilitation and obtaining a DSc degree. His research interests included the development of new synthetic methodologies, transition metal catalysis in particular, and their application to heterocyclic chemistry.

In 2007 he joined the newly established Servier Research Institute of Medicinal Chemistry as director of the Discovery Chemistry division and in 2015 he became managing director of the institute. Since 2007 he has been in charge of multiple research projects in oncology and metabolism. András Kotschy is the author of 56 refereed publications that received over 1000 citations, 1 book, 2 book chapters, and 10 patents. He is also the recipient of multiple scientific awards and fellowships.

Andres Lust

Institute of Pharmacy, Faculty of Medicine, University of Tartu, Estonia

Dr. Andres Lust received his MSc (Pharm) degree in 2010 and PhD (Pharm) in 2015 at the University of Tartu, Estonia. The title of his PhD thesis is "Water mediated solid state transformations of a polymorphic drug – effect on pharmaceutical product performance". In 2012, he received a research mobility grant from the Academy of Finland and has also acted as a researcher in several other scientific research projects. His main research areas are Pharmaceutical technology and Physical pharmacy, and the current research interests include e.g., solid-state properties of pharmaceutical substances, phase transformations, drug-excipient interactions, and electrospraying/spinning as nanofabrication techniques. Currently, Dr. Lust is acting as a Research Fellow and Scientist in the Institute of Pharmacy, University of Tartu.

Aleš Mrhar

Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia

After finishing his pharmacy internship, Ales Mrhar (PhD, MPharm) became associated with the Faculty of Pharmacy, University of Ljubljana, Chair for Biopharmaceutics and Pharmacokinetics as Assistant Professor in 1976 and Full Professor for Pharmaceutical Technology and Biopharmaceutics with Pharmacokinetics in 1994. He has worked as post-doctorate fellow at the NCTR in Jefferson (Arkansas, USA) in July 1984 and three times (September 1988, June 1990 and October 1992) at the University of Trieste (Italy). For 4 years (1991-1995) he has served as the Dean of the Faculty of Pharmacy at the University of Ljubljana and for 8 years (2001-2009) as the Head of the Biopharmaceutic and Pharmacokinetic Chair. Additionally he has been engaged from 2006 to 2008 as a visiting professor for pharmacology at the Medical Faculty of the Univeristy of Maribor. He has acted as a mentor to more than 180 diplomants, 23 specializants, 24 master degree and 17 PhD students. His research interests include development of in vitro and in vivo tests in biopharmaceutics and pharmacokinetics, development of experimental models for studying interactions, transport and metabolism of drugs in biological systems of increasing complexity, pharmacokinetic-pharmacodynamic analysis using compartmental and hybrid models, statistic and computer aided design of drug delivery systems, development of site-specific microspheres for intravesical and colonic delivery, pharmacoepidemiologic and pharmacoeconomic analysis, and finaly outcomes research (clinical, economic and humanistic outcomes in relation to drug medical treatments). Ales Mrhar is author and co-author of 167/206 articles published in international peer-reviewed journals with 1029/1288 pure citations (source: WoS/Scopus, status: 21 February 2017). He is recipient of the national award for the achievements in research on the field of mathematical modeling and computer simulation in pharmacokinetics, in 1990. Moreover, from the very beginning he has been developing strong collaboration with national and international pharmaceutical industry in terms of running more than 50 basic and applied projects in the fields of pharmaceutical technology, biopharmaceutics and pharmacokinetics, and pharmacoeconomics. He is also the member of editorial board of Acta Pharmaceutica, an international journal that publishes articles dealing with pharmaceutical sciences and related fields. Since 2001 he acts also as a guest editor of International Journal of Pharmaceutics and European Journal of Pharmaceutical Sciences. In 1996 Ales Mrhar was elected president of the Section for Pharmaceutical Sciences of the Slovenian Pharmaceutical Society. In this capacity he joined EUFEPS, European Federation of Pharmaceutical Sciences, first as a Council member, later as Committee for Congresses and Conferences member and finnaly as Executive Committee member for the term 2002-2004. At the same time he was appointed President of The Central European Symposium

on Pharmaceutical Technology and Biotechnology, which has been organized under the patronage of EUFEPS biennialy since 1995, lastly in 2016 for the 11th time in Beograd (Serbia). Since 2001 Ales Mrhar is actively involved in research and eductions activities in the area of clinical pharmacy with the aim to implement the principles of rational drug usage in healthcare systems. In this capacity he is responsible for collaboration between academic institutions and hospitals on national and international levels. He has managed more than 10 successful projects and published more than 30 articles in peer-reviewed national and international journals proving that clinical pharmacist with knowledge from the areas of medicinal chemistry, drug delivery systems, clinical pharmacokinetics and pharmacogenetics is an indispensable healthcare provider. Moreover, the results of these studies clearly show that by this support clinical, humanistic and economic outcomes are significantly improved.

Jessica Rosenholm

Pharmaceutical Sciences Laboratory, Åbo Akademi University, Turku, Finland

Jessica Rosenholm holds a docentship in biomedical nanotechnology at Åbo Akademi University, Finland, from where she also received her MSc(Tech) degree in chemical engineering in 2002. Her doctorate period included a four-year funded position in the national Biomaterials and Tissue Engineering Graduate School, from which she graduated her DSc(Tech) degree in 2008. Her thesis work "Modular Design of Mesoporous Silica Materials: Towards Multifunctional Drug Delivery Systems" has been awarded national and international prizes, e.g. the Akzo Nobel Nordic Research Prize 2009 for best doctoral thesis and research activity in colloid and surface science in the Nordic countries. In 2009-2010 she spent a postdoctoral period at the Nano Biomedical Research Centre, Med-X Research Institute, Shanghai Jiao Tong University in China. Since returning to Finland in 2010, she heads her own group, the BioNanoMaterials group. The group's activities are centered on the development of nanomedicines for drug delivery and/or imaging, for the enabling of a variety of diagnostic and therapeutic applications. The designed systems are largely based on mesoporous silica and its composite nanostructures. Since 1.1.2015 she is appointed professor in pharmaceutical development at the Pharmaceutical Sciences Laboratory, Faculty of Science and Engineering, Åbo Akademi University (www.pharmscilab.fi). Currently the group is further involved in formulating the already developed nanosystems into different dosage forms including dermal patches, antibacterial coatings and varying 2D/3D printed formulations e.g. for tissue engineering.

Sándor Szalma

Institute of Takeda Pharmaceutical Company

Sándor Szalma is senior director of biomedical informatics within the Data Science Institute of Takeda Pharmaceutical Company. Most recently, he was head of Translational Informatics and External Innovation, R&D IT in Janssen Research & Development, LLC. He serves as a member of the industry advisory committee of ELIXIR. Previously, he was member of the board of the Pistoia Alliance, member of the Translational Medicine Advisory Committee of the PhRMA Foundation and led the Data & Knowledge Management Strategic Governance Group of Innovative Medicine Initiative. His past positions included president of MeTa Informatics, general manager of QuantumBio and senior director of Computational Biology and Bioinformatics at Accelrys, Inc. He was co-founder of Acheuron Pharmaceuticals, Inc. He lectured at UCSD Extension and was adjunct professor at Rutgers University in the Computational Biology and Molecular Biophysics program. He is the author of more than 40 sci-

entific publications and book chapters and two patents. He received his doctoral degree in chemistry from A. Szent-Györgyi Medical University in Szeged, Hungary.

He is married to Judit and they have two grown up children Dániel and Dorina. They live in Carlsbad, CA, USA.

Mátyás Szentiványi

Roche Hungary Ltd. Budapest, Hungary

Mátyás Szentiványi MD PhD. graduated from Semmelweis University of Medicine and received his MD degree in 1992. He worked six years as a researcher at the same university and two years at the Medical College of Wisconsin in Milwaukee (USA). His field of interest was vascular physiology, renal physiology, and hypertension. He received his PhD degree at the Semmelweis University of Medicine in 2002. The title of his PhD thesis was „Adaptive control mechanisms of the saphenous region".

Since 2000 he works in pharma business, in the first five years at a big CRO (Quintiles), while in the last twelve years at a multinational pharmaceutical company (Roche). Currently he is the medical director of Roche in Hungary. He has broad experience in clinical research and significant medical affairs experience working in oncology, haematology, and hepatology. Current responsibilities include heading the medical department and overseeing its different units (medical affairs, clinical trials, regulatory, pharmacovigilance). Additional responsibilities include taking part in the company's leadership team and compliance board. Since 2011 he is a member of the Communication Ethics Committee of the Hungarian Pharma Associations.

Mátyás Szentiványi is first author of 6 articles in international scientific journals and second author of 5 articles. He presented 21 scientific presentations in international scientific meetings.

Main publications:

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- *Szentiványi M Jr et al. Am J Physiol 283: R266-R272. 2002*

György Thaler

Development Director, Gedeon Richter Plc., Hungary

György Thaler joined Gedeon Richter Plc in 1983 as a chemical engineer. After spending some years as a medicinal chemist he completed his Ph.D. at the Technical University of Budapest in synthetic organic chemistry. After holding different management positions he is Development Director of the Richter Group since 1992. His current responsibilities are product development and regulatory affairs. He is the chairman of the Legal Affairs Committee of Medicines for Europe, since its establishment in 2002. He is also serving as Executive Board member of Medicines for Europe.

Irem Yenice

Head of Biotechnology and R&D Director, Arven, Turkey

Irem Yenice graduated from Hacettepe University in 2007 with a Ph.D. degree in Pharmaceutical Technology. After working as a researcher at Hacettepe University, she joined Sanovel in 2007, a Turkish Pharmaceutical Generic Company of TOKSOZ Group. She has played leading roles in in the company's biosimilar program. Over the last nine years, she set up the biotechnology division for biosimilars comprising manufacturing and characterization experts. In 2014, Dr. Yenice and her team moved to ARVEN, a company of TOKSOZ Group, with a vision to develop high-tech products committing to requested quality standarts toward global recognition. Dr. Yenice and her team developed the first biosimilar of Turkey, biosimilar filgrastim, from cell line to product. She has been working as the head of Biotechnology Department and R&D Director at Arven since December 2016.

Acta Pharmaceutica Hungarica – 7th BBBB Edition – Plenary Lectures 87. 98-102 2017.

Plenary Lectures

Pl-1

Trends of drug research and development in Europe

BILENSOY, E.

President of European Federation of Pharmaceutical Sciences (EUFEPS)
Department of Pharmaceutical Technology, Hacettepe University, Faculty of Pharmacy, Ankara, Turkey

Drug research and development has been under focus since the last century globally, as the world is moving towards an aging population. In the meantime, in-depth novel techniques incorporating pharmacogenomics, allow the diseases to be better elucidated than before. This breakthrough paved the way to a more integrated approach based on systems pharmacology for drug research and development. In this lecture, new trends in drug delivery, drug development and research will be discussed in the light of recent reports and strategic research and innovation agenda from European Technology Platform. It has to be noted that drug research and drug development is becoming more and more concentrated on the patient and individualized/precision medicine is the driving force in today's pharmaceutical research in all disciplines in this field. This effect is starting to diffuse into the pharmacy practice and even more into the pharmacy education in Europe. This lecture will focus on current trends in pharmaceutical research and give an insight on EUFEPS initiatives to support these new trends in pharmaceutical research and innovation. EUFEPS is a federation of 18 member societies from different countries in Europe as well as individual members and member institutions. Based on Frankfurt Germany, EUFEPS is a an organization active in scientific events, education and training for professionals in pharmaceutical sciences, regulatory activities about medicines and medical devices with position papers and reports on drafts guidelines by EMA. EUFEPS has established Networks to bring together individuals supported by member societies on Bioavailability/Biopharmaceutics, Pharmacogenomics, Quality by Design/Process Analytical Technology, Nanomedicine, Safety Sciences, Veterinary Drugs. Systems Pharmacology and Regulatory Sciences.

Pl-2

Challenges of the pharmaceutical industry: Where are we heading?

THALER, GY.

Gedeon Richter Plc., Budapest, Hungary

Many people think that the pharmaceutical industry reached its golden era some decades ago and those opportunities we had then, will never return again. There are several factors which tend to support that statement. During the course of the presentation we will hear some of them including the investors' view and demographic changes which impacted the behaviour of social security systems (the payers). Political level influences in some countries also may effect the room for operation of the companies. The declining efficiency of the classical pharmaceutical R&D and the rise of biotech products also shape the future of the industry. What are the growth opportunities for the pharmaceutical industry today? What are the global market trends that help or are against growth? What realistic chances a mid-sized company has in Hungary to survive? What are the most pressing limitations we have? What kind of strategic directions we may consider and what are the key elements of growth? These questions will be tackled in the presentation.

Pl-3

New chemical enrtity research and development in Hungary: challenges and opportunities

GREINER, I.

Research Director, Gedeon Richter Plc., Budapest, Hungary

BACKGROUND: During the past twenty five years new chemical entity research delivered very limited results in Hungary. This was not only becasue companies would like to hide their results, if any, before their competitors, but also because academic research did not publish any related paper or article. During the last two years something started to change.

AIMS: Based ont he last two years results having listed and analysed future opportunities and trends will be discussed.

RESULTS: As it is well known from the literature Gedeon Richter plc. granted positive opinion from EMA CHMP to its original drug, cariprazine for schisophrenia indication. FDA has approved the same product nearly two years ago for the previous and one more (bipolar mania) indication. This is definitely the first drug which was discovered, and developed with different partners by a CEE company and approved on 70% of the world market [1]. Beside this result two small Hungarian companies called Avidin adn Soneas announced that phase I. study had been successfully finished with their investigational drug against cognitive disorders[2]. Last year Hungarian chemist at Servier (Budapest) publish a Nature paper [3] about a new clinical candidate and it was also revealed that a unique cooperation between academia and two SMEs resulted a clinical candidate SzV-1287 [4].

CONCLUSIONS: Based ont he latest results of Hungarian pharma R&D present position of Hungary in this field can be regarded as special in this region and further support of this inspirative environment can strengthen its role in the world pharma R&D.

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Pl-4

Supporting health market innovation by OGYEI

SZOLYAK, T.

National Institute of Pharmacy and Nutrition, Budapest, Hungary

The majority of new pharmaceutical developments, as well as innovations in the fields of medical devices and health-focused nutrition products are initiated by academic research groups. However, translating basic research into applied research is often problematic. Realizing this challenge has inspired the foundation of the EU Innovation Network, and the Innovation Office of OGYEI as one of the first innovation offices established by European pharmaceutical agencies. The Innovation Office aims to support early developmental programmes in order to promote that research groups execute their innovative approaches. Upon developing the core concepts of the Innovation Office we have realized that the scope of our activities should be widened to include providing advice to pharmaceutical companies, and also supporting that developers get a better access to the resources offered by the European Medicines Agency. Besides, the Innovation Office is aimed to serve as a methodological centre of OGYEI, and hereby aims to foster conversation between Hungarian stakeholders committed to health development.

Pl-5

Restoring programmed cell death – a new approach in cancer therapy

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Tumour cells that harbour genetic mutations and are recognised as abnormal should be naturally eliminated but they maintain their existence by a combination of multiple activities – also known as the hallmarks of cancer. One of these hallmarks is the evasion of apoptosis, the programmed cell death. The restoration of the apoptotic cascade in tumour cells has long been recognised as a promising way to treat cancer but the major members of this protein family, BCL2, MCL1, and BCL-xL have long remained elusive targets decades long for drug discovery. Recently the decade long efforts of the pharmaceutical industry have been rewarded by the identification of potent and selective inhibitors for some family members.

The presentation overviews the principal pharmacological and chemical challenges of targeting this protein family and presents the recent scientific [1] and pharmacological achievements in this area.

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Pl-6

Next generation sequencing: the future of personalised healthcare (PHC 2.0)

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Innovative drugs significantly contribute to the success of our healthcare including to the fight against cancer. Some drugs act in specific patient populations which require different diagnostic tools. This is called Personalised Healthcare (PHC) where a given proportion of the patients can be chosen who will have better chance to respond to a given drug. Evidence shows that personalised targeted therapies are associated with significantly better outcomes than cytotoxic agents. However, this approach is unable to treat a significant portion of the patients and many patients do not have access to novel diagnostics and medicines. Therefore a new method is necessary to give an even higher chance to cancer survival with a good quality of life. The technology of Next Generation Sequencing (NGS) combined with setting up new databases enables us to find the ways how a single patient can be treated. With NGS more genetic alterations associated to different cancer types can be found than with single gene testing, the current method. This is called PHC 2.0 which provides new treatment options to 70 % of the patients including off-label use of current treatments and targeted enrollment into clinical trials. This latter can improve the recruitment of the trials resulting in faster and more accurate drug development which will save money for the society. In addition PHC 2.0 shows to appr. 10 % of the patients that no current treatments are available for them saving them from the side effects and other complications of any drug currently available on the market. In conclusion, new genomic sequencing technology (NGS) together with advanced bioinformatics and reporting are available to help physicians understand patient tumour profiles and improve personalised patient care.

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Pl-7

"It is in your hands" – How healthcare professionals can ensure their safety when handling hazardous drugs

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BACKGROUND

Handling chemotherapy drugs constitutes high risk to the healthcare professionals. Compounds with carcinogenic, mutagenic, reprotoxic (CMR) potency should fully be removed from work environments. Unfortunately, these carcinogens do not have a defined safety level. Depending on individual sensitivity, one molecule may cause a serious and irreversible health impact. Assessing environmental contamination and keeping it below detection limits are critical.

AIMS

To assess contamination due to cytotoxic drugs in hospital pharmacies, to evaluate the efficacy of a Closed System Transfer Device (CSTD, Tevadaptor) in reducing cytotoxic contamination and in preventing pharmacy staff from exposure of hazardous drugs.

RESULTS

We carried out a study in 13 Hungarian Hospitals where cytotoxic drugs prepared using the traditional needle/syringe methods and then using a CSTD (Tevadaptor) to assess the difference in levels of contamination in main areas, such as vial surface, laminar box - preparation area, infusion bag surface, gloves of pharmacists. Two sets of wipe samples were taken following the ESOP study protocol: the first to establish baseline contamination and a post intervention measure to assess the efficacy of Tevadaptor to reduce environmental contamination. The samples were sent to a validated laboratory (IUTA in Duisburg, Germany) for chromatography analysis. Higher levels of contamination were found at baseline, while using CSTD (Tevadaptor) to manipulate cytotoxic drugs significantly decreased contamination.

CONCLUSIONS

Contamination was reduced to below the level of detection after a CSTD (Tevadaptor) was implemented and both the environment and healthcare professionals remained contamination free. These results showed that the use of a CSTD in handling hazardous drugs is highly recommended.

Pl-8

Biosimilars landscape – Development, regulatory & market access challenges

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The past decades have seen the breakthrough of biologics within the pharmaceutical sector. As many of these blockbuster biological products' patents expire, there is an enormous opportunity for biosimilar products to make these, often life-saving, medicines accessible to considerably more patients, particularly in the fields of oncology and immunology.

The objective of the presentation is to give an overview of biosimilar products, their development challenges, the regulatory requirements they must adhere to and a view of their market potential.

Development and manufacture of biologics is very different to traditional small molecule pharmaceuticals. Stable expression of large protein molecules and their purification are the key challenges for drug substance development and manufacture. Most biologics are parenteral products requiring appropriate final formulation development and specific fill & finish manufacturing technologies.

The precise characterisation of biologics poses an exciting challenge for analytical teams the world over, and is of pivotal importance in the development of biosimilars. In fact, the very stringent regulatory requirements applied to biosimilar developments are in part due to the difficulty posed in precise characterisation of such macromolecule based medicines. Significant clinical development programmes are expected of biosimilars, very differently to small molecule generic developments.

Further to development and regulatory challenges, market access requirements also differ and present new challenges as well as opportunities for companies with biopharmaceutical portfolios.

Development, manufacture and commercialisation of biologics, including biosimilars, have a higher entry barrier than small molecule developments due to differentiated know how requirements, high capital investment, development and manufacturing costs in addition to changing regulatory and commercial landscapes.

Pl-9

Focus on biosimilar filgrastim development

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Biological medicines are made by or derived from a biological source, such as a bacterium, yeast or mammalian based cells. The active substances of biological medicines are larger and more complex than those of non-biological medicines. Development of biosimilars is much more challenging than generic small molecules due to their complexity of structure and manufacturing processes and their potential risks for increased immunogenicity. Therefore, specific regulatory approval pathways and guidelines must be followed during the development of biosimilars. Determination of the biosimilarity is based on the comparison of the candidate biosimilar product and its reference product with respect to structure (by using chromatographic, electrophoretic techniques , function (receptor binding and bioassay studies, etc), animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness. A rigorous scientific process for an evaluation of potential differences between candidate biosimilar product and its reference product is essential to ensure quality, safety and efficacy of the biosimilar. This presentation will focus on a Arven's first biosimilar product (biosimilar filgrastim) and it's development history. Detailed manufacturing processes, in-process controls, material and product testing, also structural and functional in vitro characterization studies including physical, chemical, biological tests, and comparative studies against the reference licensed drug product, will be presented. Non-clinical studies including in vitro and in vivo biological studies, and toxicokinetic study with biosimilar filgrastim, prior to initiating clinical development were carried out in accordance with related EMA guidelines.

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Pl-10

Target and biomarker discovery in an open ecosystem

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One of the most important characteristics of a successful drug discovery enterprise is to be able to develop a treatment for the right target for the right disease and for right population. An additional aspect is that the developed solution has to be competitive and commercially viable so that the commercial success provides the means for the pharmaceutical enterprise to continue its R&D and commercial operation. The Data Science Institute has been on the forefront of transforming the practice of drug discovery and development within Takeda Pharmaceutical Company. Our R&D leadership is committed to explore ideas in a very open, pre-competitive biomedical ecosystem. By converging external and internal best practices, we strive to renew the pipeline of novel potential treatments for multiple therapeutic areas of focus such as CNS, gastroenterology and oncology. We are championing two main concepts. Sustainable target selection is the first step – we should start by inspecting the heterogeneity of medical practice and patient pathways across target markets and to understand regulatory and market conditions so that the selected targets can be sustained through the arduous road of drug development and regulatory approval. The other concept is to apply a multimodal approach to biomarker discovery so that the right disease and right population can be identified. We are generating deep biomolecular and phenotypic data from patients, harmonize and standardize the practice of data collection and processing and research novel algorithms and methods to extract meaningful information to enable evidence-based decision making. In this talk I will present several use cases describing how we transform the wealth of evidence derived from internal studies, academic collaborations, public-private partnerships and pre-competitive consortia into insights by applying machine learning and advanced analytics and informatics tools.

Pl.11

Translational medicine taking discoveries to patients benefits

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Translational medicine forms a bridge between clinical and basic research. It is an umbrella term for 'translating' preclinical research findings to everyday clinical practice and patient care, thus going from bench to bedside. It also involves experiments that facilitate a better understanding of the development of diseases within basic research, the discovery of pharmaceutical points of attack, effect studies applicable to human therapies, the biological study of human diseases and new improvements in treating human diseases. It also includes non-human or non-clinical studies, which can even form the foundation for new clinical applications and drug development trials in clinical phases 1–3. In the 21st century clinical medicine should be divided into two main categories: general and translational medicine. The central work of general medicine is to provide basic care and graduate training, while translational medicine – besides the good care - engages in clinically-oriented studies (thus increasing scientific output), pharmaceutical phase trials (to discover new therapies and grow institutional income) and postgraduate training (to raise the number of PhDs and other academic degrees). Patients are only affected by translational medicine if they undertake to participate in a clinical study (based on the National Institutes of Health (NIH) model). Another feature of the system is its multidisciplinary nature; that is, it facilitates theoretical and clinical research in particular medical specialties in coordination with various fields (IT, mathematics, clinical research, theoretical research and management). In this lecture I will drive through the audience from the bedside to the laboratory and backwards by presenting our recent discoveries in acute pancreatitis.

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Oral presentations

O-1

Design and synthesis of novel inhibitors targeting pathogenic protozoan parasites

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Malaria and leishmaniasis are caused by protozoan parasites that are responsible of major morbidity and mortality across the world, and new specific therapies are greatly needed. Several of the diseases associated to protozoan parasites are classified as "neglected diseases" by The World Health Organization (WHO). The protozoan parasites also cause health problems in developed countries, e.g. *Toxoplasma* causes congenital toxoplasmosis and infections in immunosuppressed individuals. Membrane-bound pyrophosphatases (mPPases), which have no human homologs, are essential in parasites. It was recently shown that mPPases present in protozoan parasites have a unique molecular structure.[1] They are thus ideal drug targets.

At present, there are no pharmacologically relevant inhibitors for mPPases.[2] Here, our recently identified hit compounds will be presented for the first time. We decided to optimize one of the four mPPase hit compounds to improve the binding activities and to enhance the drug-like properties. Furthermore, in-house compounds yielded three more compound classes that showed inhibition of mPPase. To date, we have developed novel compounds showing IC_{50} values between 1 and 10 μM. These inhibitors have been subsequently screened against *Plasmodium* and *Leishmania* species, and preliminary results show that the best compounds inhibited *Plasmodium falciparum* with IC_{50} values of 7-19 μM, and *Leishmania donovani* with GI_{50} values of 0.6-22 μM. Furthermore, cytotoxicity studies showed that these compounds are well tolerated. These compounds will be further improved with medicinal chemistry tools into viable lead compounds showing favorable drug-like properties. Subsequently, the inhibitors will be validated in *in vivo* animal models. Therefore, the ultimate goal of this ground-breaking project will be novel drug-like inhibitors of pathogenic protozoan parasites.

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O-2

Exploring protein kinase CK2 by designing heterocyclic compounds

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BACKGROUND: There is considerable international attention related to new inhibitors of casein kinase 2 (CK2), a highly conserved serine/threonine protein kinase that is playing a key role in cell growth, proliferation and regulation of apoptosis.[1] Inhibition of CK2 kinase activity is become an attractive way to stop growth of cancer cells (e.g. glioblastoma, renal cell carcinoma, acute myeloid leukemia). In parallel, our academic Group mainly develops synthetic methods that provide access to biologically active compounds. Then we progressively optimized the relationships between structures and activities for CK2.[2]

AIMS: The objective of our study is to use and functionalize diverse chemical scaffolds according to the structural features of CK2: ATP-binding site, CK2alpha-CK2beta interface, allosteric sites.

RESULTS: Indeno[1,2-b]indoles, aminothiazoles and indoles were used and developped to target CK2, with the use of an international MedChem toolbox.

CONCLUSIONS: The presentation presents diverse strategies for the development of new bioactive small molecules as CK2 inhibitors. Sharing research also allows efficient work...

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O-3

Stereoselective synthesis, synthetic and pharmacological applications of chiral aminodiols and diaminoalcohols

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BACKGROUND: Although pharmacologically active aliphatic aminodiols and diaminoalcohols have been studied intensively, less attention has been paid to the alicyclic analogues, even though they are useful synthetic building blocks for the synthesis of 1,3-heterocycles. Chiral aminodiols can also be successfully applied as catalysts in enantioselective syntheses.[1]

AIMS: The goal of present lecture is to summarise and overview the latest results on the field of the synthesis and application of 3-amino-1,2-diols and diaminoalcohols, building blocks prepared from natural sources.

RESULTS: The synthesis of chiral aminodiols followed two strategies: nucleophilic ring opening of monoterpene-based epoxyalcohols or OsO_4 catalysed stereoselective dihydroxylation of protected allylic amines. Diaminoalcohols were prepared starting from pinane-based protected allylamines via stereoselective epoxidation followed by aminolysis of the resulting oxyrane ring. Each synthesis was started from commercially available natural monoterpenes, as chiral sources. Regioselectivity of ring closure of aminodiols was also studied in detail.

CONCLUSIONS: The obtained monoterpene-based tridentate ligands were applied as chiral ligands in the enantioselective addition of diethylzinc to aromatic aldehydes. Monoterpenic aminodiol-based nucleoside analogues were investigated as highly selective novel NCX (sodium–calcium exchanger) inhibitors.

This work was supported by Hungarian Research Foundation (K112442).

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O-4

Continuous-flow solid-phase synthesis of peptides with exceptionally low amino acid consumption

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BACKGROUND: The importance of synthesis of peptides is warranted by the need for peptide-based medicines. Nowadays, peptide synthesis is performed almost exclusively on solid supports. The solid-phase peptide synthesis (SPPS) technique has subsequently been progressively developed. However, still a general drawback of these methodologies are the high number of amino acid equivalents required for total coupling.

AIMS: Continuous-flow (CF) approaches have recently gained in significance among synthetic techniques. We show here that the number of amino acid equivalents used for SPPS can be lowered drastically to around 1.5 equivalents through the application of a CF technique and by complete reaction parameter optimization.

RESULTS: Under the optimized conditions the couplings of all 20 proteinogenic amino acids with 1.5 amino acid equivalents proceeded with excellent conversions. To demonstrate the efficiency of the CF-SPPS methodology, known difficult sequences were synthetized in automated way. The purities of the resulting crude peptides were comparable with literature result, but the CF-SPPS methodology requires much less amino acid and solvent. As further evidence of the effectiveness, β-peptide foldamers, N-methylated peptides and protected sequences were synthetized in excellent yields.

CONCLUSIONS: A highly efficient CF peptide synthesis technology was developed. Importantly, exotic and expensive artificial amino acids were incorporated into sequences by an automated way through the use of exceptionally low numbers of amino acid equivalents at low costs, thus the synthesis of such sequences was carried out by a considerable cheaper way.

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O-5

Homochirality of β-peptides: a significant biomimetic property of unnatural systems

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BACKGROUND: Homochirality, an interesting phenomenon of life, is mainly an unresolved problem and was thought to be a property of living matter. Numerous investigations have been carried out by several scientists in case of natural α-peptides.[1] Foldamers are artificial self-organizing systems, display considerable tendency to form high stable and versatile secondary structures, e.g. helices, strands, turns. The most prominent representatives of these oligomers are the β-peptides of which possess additional biomimetic properties mimicking natural α-peptides. In case of beta-peptides the stereodiscriminative chain-elongation is still ambiguous compared to natural α-peptides.[2]

AIMS: Our aim was to investigate how the secondary structure can affect the stereochemical course of the homochiral oligomer formation in the stereochemically discriminated synthesis of β-peptides with various side-chains shape and secondary structures in order to gain some insights into the origin of biological homochirality.

RESULTS: The preliminary results show, that there is a strong propensity for homochiral homooligomer formation. Furthermore, we found that the diastereoselecivity increases in the presence of water which can be explaining due to the water induced self-association of peptides. Noteworthy, the diastereoselecivity was chain-length dependent.

CONCLUSIONS: We conclude that the biological homochirality as a biomimetic property is also occurring with unnatural compounds, like β-peptide foldamers. We confirmed that the self-association of peptides is a crucial fact behind the homochirality phenomenon.

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O-6

Hypothesis driven versus Genome Wide Association Studies: Which one is more relevant for precision medicine?

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With the revolution of our knowledge and genotyping techniques deep genotyping through GWAS (Genome Wide Association Studies) and NGS (Next Generation Sequencing) methods became preferred against traditional methods like hypothesis driven candidate gene studies. The gap between GWAS and candidate gene studies is becoming continuously wider. Theoretically GWAS offers a favourable hypothesis free approach that is relatively inexpensive and allows to collect data of tens of thousands patients and controls. Limitations are also evident, namely, only a few genome-wide significant hits emerge, and even these risk variants are present only in an extremely low rate in the patient population. An even more significant problem is that we do not take into account personal details of the patients, such as specific symptoms, case history, detailed drug responses or environmental factors. For precision medicine we have to separate patient groups for different treatment regimens. The separation could be performed on the basis of genetic variants, phenotypic measurements (e.g., symptoms), environmental factors (e.g., exposure to drugs, stressors) or a combination of these. Although traditional medical thinking suggests that these parameters could be used as distinct entities, there is accumulating evidence that these parameters strongly interact with each other, and therefore a useful classification and also the assignment of each individual requires all these information regarding each person. For example, genes do not directly affect the development of common disorders, but rather modify the effect of risk environmental factors leading to disease symptoms in susceptible individuals.

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O-7

Characterization of the bacterial winged-helix domain of RecQ helicase. A novel antibacterial target.

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BACKGROUND: Nowadays, most of the clinically relevant antibiotics are small molecular enzyme inhibitors, and the increasing appearance of multidrug resistant bacteria is becoming an urgent problem. Inhibiting bacterial protein-protein interactions may provide a new tool for fighting against resistant strains, since developing point mutation on one target molecule is not enough for survivability. Artificial beta-peptide foldamers provide a good option due to their high molecule surface/atom number ratio, and potentially long half-life *in vivo*.

AIMS: A well-studied interaction between *E. coli* RecQ winged helix domain and the C-terminal 8 amino acids of single-stranded DNA-binding protein (SSB) was described using NMR, provides a good model for studying this phenomenon (1). In order to study this interaction the recombinant production of RecQ winged helix domain was necessary.

RESULTS: Gene coding RecQ-WH was amplified from *E. coli* DH5α using PCR reaction, and was cloned into pET28 expression vector. The protein was overexpressed in *E. coli* BL21(DE3) strain, the system was optimized for M9 minimum media for further possible isotope labelled protein production. Ni-NTA affinity chromatography was used as first purification method. Second, the eluted protein samples were applied to cationic ion-exchange chromatography. Lastly, RecQ-WH was further purified by size exclusion chromatography. Thereafter, in order to map the protein, a pulldown assay was performed using a beta-peptide foldamer fragments (2) in the presence or in the absence of the previously synthetized SSB-C-terminal peptide. The foldamer fragments (H12 or H14 helices) contained aromatic, polar, apolar and charged groups on their proteogenic surfaces. The protein was found to bind different H12 and H14 helices.

CONCLUSIONS: Further analysis of the interaction is needed between the protein and the selected foldamer helices. Dissociation constant of each foldamer helix must be determined using ITC. The best binders, and the nature of the interaction are going to be investigated in NMR using isotope labelled protein.

The work was supported by Foundation for Development of Pharmacy Education at University of Szeged.

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O-8

Nanoscale analysis of prostate cancer tissue microarrays

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BACKGROUND: Cancer is the leading cause of death in the developed countries. Detecting alterations at the molecular level linked to cancer is a key aspect in developing new strategies for treatment and for diagnosis. For this purpose tissue biopsies are analyzed using various analytical techniques, such as mass spectrometry, and may result in the identification of novel biomarkers. Tissue microarrays (TMAs) contain a large number of biopsies prepared in an array format. The use of TMAs in biomedical workflows is significantly increasing in the past few years; the main challenge is the limited amount of sample available (1.5 mm diameter cores).

AIMS: The aim of our work is to apply advanced nanoLC-MS(MS) techniques to reliably identify various glycans and proteins from histological tissue surfaces and to apply the workflow for the analysis of prostate cancer TMAs. Integrating proteomics data with glycan analysis has recently become widespread. Glycosaminoglycans (GAGs) play crucial roles in cancer progression; however, their nanoscale analysis is still considered an analytical challenge compared to proteomics methods, which are relatively straightforward.

RESULTS: Proteins and GAGs were analyzed using nanoLC-MS(MS) following enzymatic digestion and extraction from the surface of prostate cancer TMA slides. More than 500 proteins were identified and quantified using label free quantitation from the 1.5 mm diameter cores, including several proteogly-

cans (e.g., perlecan, versican, lumican) that had been previously implicated in prostate cancer. For the analysis of the GAG disaccharides self-packed nanoscale HILIC-WAX columns were packed and negative ionization mode was used. Strategies for the analysis of the limited amount of GAGs extracted from the surface of TMAs will be shown.

CONCLUSIONS: Label free quantitation showed that the amount of proteoglycans was increased in cancer. Limited amount of GAG chains were successfully analyzed from TMA slides.

O-9

Analytical sciences: serving the changing pharmaceutical landscape

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The pharmaceutical industry subsists in a highly regulated environment where the regulatory and/or the GMP requirements set the standards higher in all related field in order to ensure efficacy, production consistency as well as to minimize patient risk under very competitive conditions. Analytical sciences serve the background of the pharmaceutical development from API/reference product characterization, to product development including excipient and packaging selection and stability studies. Thus, the recent developments in the pharmaceutical landscape (continuous technology, biosimilar development, QbD technology development) need to be served by a well selected analytical arsenal. The present talk will show selected examples (without intended to be comprehensive) from the field of the above mentioned areas with special focus how the correctly chosen analytical tool can speed up development. Finally the expense of such analytical solutions will also be discussed as "there is no free lunch" as the proverb says.

O-10

Triple quadrupole or high resolution accurate mass: the quantitation conundrum

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For over twenty five years, triple stage quadrupole (TSQ) mass spectrometers have been the default analytical instrument used in routine laboratories for accurate and precise, sensitive detection. The reason for this is based on the selectivity of TSQ instruments when operated in selective reaction monitoring (SRM) mode, providing the user with high quality data, which can be reported with confidence.

There are however analytical challenges where TSQ mass spectrometers are not necessarily capable of providing the quality of data. This can be for many reasons, which one might address through sample preparation or chromatography. If however there are still issues, the desired sensitivity, or more accurately signal to noise, might not be achieved.

With the advent of simple, user friendly high resolution accurate mass (HRAM) instrumentation such as the orbitrap, the analyst has another option to achieve the desired high quality sensitive data with confidence. With the use of HRAM, the user is able to achieve and often exceed the level of selectivity observed with a TSQ. This is particularly advantageous where fragmentation of compounds is problematic, or where there are issues with matrix interference.

Orbitrap based instruments are being increasingly accepted as complimentary to TSQ instruments in the routine quantitation laboratory, expanding the tool set available to the analyst. The presentation will focus and explore the use of TSQ and HRAM Orbitrap instruments for highly sensitive, robust and reproducible analysis in the routine laboratory.

O-11

Development and manufacture of biosimilar medicinal products

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BACKGROUND: Successful development and manufacture of biological medicinal products requires specific knowledge from both the development and manufacturing teams.

AIMS: One of the final objectives of any biopharmaceutical development is to develop a formulation and manufacturing process, which result in stable drug products suitable for regulatory submission and market entry. The two presentations will give an overview about the entire develop-

ment process illustrated with examples and their relevance regarding final drug product quality.

RESULTS: Information coming from the development phase supports designing plant scale drug product manufacturing procedures, however technology scale-up poses its own unforeseen challenges in the process of finalising the manufacturing technology. Product development focuses mainly on factors influencing protein stability and protein degradation. Formulation, compatibility and stress studies are all important aspects to take into account during development. GMP and other regulations have to be taken into consideration while planning the manufacturing procedure in plant scale. Development and manufacture of biosimilars requires considerable analytical support including a wide range of analytical methods. Another important aspect is that development of drug substance and drug product manufacturing technology have to proceed in parallel with analytical method developments. However, differences between drug substance and drug product are less pronounced in the case of parenteral biologics than in the case of many small molecule pharmaceuticals.

CONCLUSIONS: Development of biopharmaceuticals needs to consider physico-chemical, biochemical, biological, clinical, regulatory, GMP, marketing and financial aspects all at the same time. Drug product development and manufacture are impacted by drug substance development and proceed hand in hand.

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O-12

Innovative approach to improve the film coating efficiency with applying of a continuous film coater

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BACKGROUND: Increasing market need to coat sensitive products and flexibility in batch size are major challanges to be considered during the development and manufacturing of coated tablets.

AIMS: A new project had been initiated to build up a new internal approach to improve the efficacy and quality of non-functional coating processes with possibilities to support the special market needs. Key elements of the project was the installation of a new machine with the following characters: different batch sizes can be coated without extensive scale up studies, adequate for short coating time to treat the heat sensitive products, gentle coating must be available and short changeover between batches is required to shorten the time of the campaigns. Establishment of a new internal Ways of Working was also aimed.

RESULTS: O'Hara FCC 75 continuous coater had been installed. It is the first and currently the only this pilot size machine in EU Pharma sector. New approach had been effectively developed and applied for different purposes. Soft tablets had been successfully coated with high quality. Tablets containing heat sensitive active were treated without the unacceptable degradation of the API, since the coating time was very short for the individual tablets. A comparative analysis of the time demand of a manufacturing campaign was carried out and the results exhibited relevant saving of time with the same order of magnitude energy consumption.

CONCLUSIONS: Using of unique continuous coater is advantageous for tablets suffering heat and mechanical sensitivities. Quality of these products is enhanced. Time and energy consumption of the new system and the related approach are more effective than for the existing pan coater system. The new approach is an exceptional opportunity to change and reorganize the existing products/processes. The associated flexibility can be improved by the modification of batch/campaign sizes without any related development activity and cost.

O-13

A novel insight into Fluid Bed Melt Granulation: Temperature mapping for the determination of granule formation with the In-situ and spray-on techniques.

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BACKGROUND: Fluid Bed Melt Granulation has received wide interest in the research field due to

its use of binders with low melting points, which makes the drying phase of the granulation unnecessary and hence proposes a more time and energy friendly process.

AIMS: The aim of this study is to give an approach to the conditions established in a conical fluid bed granulator during the In-situ and Spray-on techniques. The determination of temperature mapping will allow the characterization of the critical zones during the melt granulation and the prediction the thermal behavior of the meltable binders. Hence identify the physical state transitions and the optimal growth mechanism areas. Two grades of Polyethylene Glycol (2000 and 6000) were used as meltable binders in three binder spraying rates and droplet sizes.

RESULTS: The treatment of data matrixes of temperature made their mapping possible by using the "Contour" function in Matlab software (1). The results showed the presence of intense heat exchange in the bottom of the bed during the In-situ technique where the binder is added in a solid state. The zone is delimited by a yellow band enabling the identification of the transition between the different heat transfer zones. The shape of the zone had a characteristic flame shape expressing the hot stream air profile. The results showed an important heating zone under the spraying nozzle for the Spray-on technique, which can be identified as the melting zone. The shape of this zone depends on the process conditions applied. The particle analysis of the final product showed more spherically shaped granules using Spray-on than In-situ due to the spherical shape of the drops.

CONCLUSIONS: The determination of temperature profiles enabled the characterization of the critical melting zone and the conditions needed to establish the optimal design space for the suitable quality attributes of granules.

The work was supported by Foundation for Development of Pharmacy Education at University of Szeged.

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O-14

Application of solid nanoparticle as emulsifiers and surface modifiers in controlled drug delivery

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BACKGROUND: Poor water solubility of drugs is a well-known problem to people involved in pharmaceutical sciences. Because of their clinical and economic significance huge effort has been made to develop new strategies to enhance their solubility and bioavailability. The preparation of drug nanocrystals suspensions and nanoemulsions with lipophilic drug dissolved in oil phase are methods with a proven ability to enhance these properties (1). In both cases amphiphilic molecules are used to stabilize the structures responsible for enhanced solubility and bioavailability. Drug release from this formulations is determined by enhanced solubility or partition coefficient, because the stabilizing layer of amphiphilic molecules do not form a diffusion barrier for drug molecules (2). The stabilization of drug nanocrystals or emulsion droplets can be achieved by adsorption of solid nanoparticles on the lipophilic-water interface. The self-assembled layer of solid nanoparticles forms a diffusion barrier for drug molecules, and the diffusion gap can be controlled by fine tuning of size and surface properties of solid nanoparticles.

AIMS: Our aim is to prepare self-assembled layer of solid nanoparticles as engineered diffusion barrier for controlled drug release, and evaluate their drug release properties.

RESULTS: For this purposes a series of silica nanoparticles with controlled size have been synthesized and used as stabilizing agent in preparation of drug nanocrystals suspensions and nanoemulsions of Indomethacin model lipophilic drug. The self-assembly is driven by attractive electrostatic forces between oppositely charged particles. The surface charge of solid nano particles have been controlled by chemical surface modification and ionic strength adjustment.

CONCLUSIONS: Preliminary test shows a

strong correlation between applied stabilizing solid nanoparticle size and dissolution properties. For time being we are working on the experiments, and the final results and conclusion will be shown at the conference

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O-15

Recent advances in Continuous Coating Technology

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Overview of Continuous Coating equipment and techniques using a novel tablet coating technology developed for high speed coating - Opadry® QX. Focusing on the Thomas Engineering CTC and ConsiGma™ coater and the Driam Conti coater. The studies looked at critical process parameters and their effect on coated tablet critical quality attributes using Opadry® QX. Placebo tablets, were coated and assessed for color development and uniformity, surface roughness and gloss. Coating with Opadry QX on the Thomas Engineering CTC and ConsiGma coater and the Driam Conti coater was successful over a wide range of conditions giving excellent color uniformity smoothness and gloss.

O-16

JASCO solutions for separation and purification of pharmaceutical compounds with carbon-dioxide

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Is Supercritical Fluid Chromatography a „New Technology"? Of course not; SFC looks back to a history of more than half a century, and has got into the focus of interest from time to time. It has proven to be a mainstream technology for chiral separations based on it is higher efficiency, throughput, and wide applicability. Chiral SFC has lately attracted increased interest and applicability, in some cases, becoming the method of choice. These are the most well known application fields. In this presentation I should like to show a few non-common applications for separation and purification using carbon-dioxide. The coupling with other analytical technics (SFC-SFE, SFC-FT-IR) results in a combined system and brings more reliable results. Simultaneous analyses of acid, neutral, basic, lipid and amphoteric substances being almost impossible to execute by conventional HPLC instumentation can be done using SFC. Column screening is a useful function in the method development for chiral substances. The stacked injection method helps to turn combined preparative systems into high-throughput ones. The JASCO SFE/SFC/HPLC „three in one" versatile system is able to give reasonable solutions, as shown by the mentioned examples.

O-17

Multimodal nanoantibiotics for synergistic modes of action against infectious diseases and for biofilm treatment

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The current global threat of increasing antimicrobial resistance (AMR), termed the "post-antibiotic era" by the WHO, as well as the recalcitrant nature of biofilm-associated infections call for the development of alternative strategies to treat bacterial diseases. Nanoparticles (NPs) have been recognized as one of the emerging and promising platforms in this respect, due their unique physical and chemical properties, which provide fine-tuning of their interactions with bacteria. Antibacterial NPs, "nanoantibiotics", can be designed to treat infectious diseases more effectively than conventional antibiotics by making use of their advantageous properties known from other nanomedical fields. These include improved pharmacokinetics of incorporated drugs, site-targeted delivery, sustained or controlled release, improved drug stability and dissolution, and so forth. The perhaps most advantageous property of nanoantibiotics in combating AMR is the possibility to construct multimodal NPs, providing synergistic actions [1] while making it difficult for bacterial cells to become resistant. Namely, the thus incorporated multiple simultaneous mechanisms of action would, likewise, require multiple simultaneous gene mutations in the same bacterial cell for AMR to develop [2]. We have constructed nanoantibiotics out of organic & inorganic components composed of an antibacterial core material (metal or

metal oxide) surrounded by a mesoporous silica shell in which antibiotic drugs are incorporated, coated with an antibacterial polymeric layer. The extent of *in vitro* bacterial growth inhibition caused by the produced nanoantibiotics has been investigated, whereas *Drosophila melanogaster* (fruit fly) has been used as an *in vivo* animal model to study the antibacterial activity of the nanoantibiotics in the gastro-intestinal tract. The observed results revealed that multiple antibacterial constructs in the designed system can improve the antibacterial activity in a synergistic fashion.

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O-18

Design and development of antimicrobial fibrous dressings for advanced wound care

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Chronic wound infections are responsible for considerable morbidity and increased healthcare costs. Recently, it has been recognised that biofilm formation is one of the main problems associated with chronic wounds and persistent infections causing delayed healing. The current therapies to treat bacterial infection in the wound rely mostly on the systemic administration of antibiotics, but the related major concerns are the risk of toxicity during treatment and insufficiently low local drug levels in the wound[1]. Alternative topical pharmaceutical formulations however require frequent application and are ineffective in the presence of wound exudate or biofilm. Therefore, there is a need to find better treatment options for infected wounds.

We have started to develop antimicrobial-loaded electrospun dressings for local wound care. Electrospun fibers have several characteristics that favour their use in such application including (i) ability to mimic the fibrillar structure of natural extracellular matrix, (ii) the high surface area to volume ratio, (iii) interconnecting porous structure with high permeability, and (iv) the ability to incorporate drugs and/or growth factors[2]. The talk will shortly cover the reasons for wound infection development and its current treatment options. Then electrospinning (ES) state-of-the-art will be reviewed. We show that the ES and its recent advances (e.g. ultrasound-enhanced ES, USES) enable to design and prepare various antimicrobial medicated fibrous dressings. Deep solid state analysis, texture analysis, *in vitro* biofilm/cytotoxicity and drug release tests enable to understand the physicochemical and mechanical properties as well as antimicrobial/antibiofilm efficiency and safety of the developed mats. This knowledge is important for the development of novel antimicrobial fibrous dressings intended for advanced wound care.

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O-19

Nanofibers – a promising delivery system for beneficial bacteria

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BACKGROUND: In the recent years, bacteria generated considerable research interest as a powerful weapon against various diseases. The fundament for their effectiveness is the number of viable cells incorporated in a patient friendly drug delivery system (1).

AIMS: In our study, the main focus was encapsulation of model bacteria in form of vegetative cells or spores into different kinds of hydrophilic nanofibers, presenting one of the newest and very promising nanomaterials. The effect of electrospinning parameters on bacterial survival during electrospinning process as well as storage conditions were closely monitored since they have been rarely studied in the past.

RESULTS: Prepared nanofibers were beadless with average diameter below 300 nm. The vegetative bacterial cells as well as spores were successfully encapsulated within nanofibers (10^{10} CFU per gram of nanofibers), visible in SEM images as local widening of nanofibers in the shape of bacteria. The results revealed that vegetative cells could not survive in hypotonic solution used for nanofiber preparation, whereas the same bacterial strain in form of spores showed high resistance against

hypotonic or acidic conditions, high voltage, and dehydration during electrospinning. Over 90% of spores remained vital after electrospinning and 2-month storage at room temerature.

CONCLUSIONS: Nanofibers represent an attractive drug delivery system for various drugs as well as for live microorganisms, as shown in our study. Furthermore, the results clearly show that incorporation of spores is a successful approach for preparation of elecrospun nanofbers with sporogenic bacteria, since it assures high bacteria viability after the electrospinning process and storage

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O-20

Development and characterization of self nanoemulsifiying systems for oral delivery of peptides

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BACKGROUND: Self emulsifiying drug delivery systems (SEDDS) are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants which form oil-in-water (o/w) emulsions in gastrointestinal tract by mild agitation. SEDDS can be used for formulation of peptides to improve bioavailability (1). In this study, ethyl oleate was used as oil phase, whereas Cremophor EL® and absolute alcohol were used as surfactant and co-surfactant respectively. Pseudoternary phase diagrams were established by titration. Surfactant/co-surfactant (S/co-S) was optimized using the following ratios: 1:1, 2:1, 3:1, 4:1 according to the pseudoternary phase diagrams. For further studies, a nanoemulsion composition was chosen around the center of gravity for the clear nanoemulsion formation (2). Statistical analysis were evaluated by one-way repeated measures ANOVA.

AIM: The aim of this study was to develop self nanoemulsifying system for oral peptide delivery. SEDDS were characterized for emulsification time, droplet size, polidispersity index (PDI) and zeta potential under storage conditions for one month.

RESULTS: The emulsification time of formulations were below one minute with bluish white appearance referred as Grade B. The mean size, PDI and zeta potential of nanoemulsion ranged between 20-50 nm, 0.1-0.2 and -7 to -20 mV respectively. During one month, the optimized formulation displayed no significant changes in both droplets size, PDI and emulsification time ($p>0.05$).

CONCLUSION: In conclusion, the ratio of oil:surfactant:co-surfactant (30:52.5:17.5) was selected for SEDDS formulation.

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O-21

Radiolabeling of targeted self assembled nanoparticles for positron emission tomography

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BACKGROUND: A biodegradable polymer based self-assembled nanoparticle family was developed by our partner, BBS Nanotechnology Ltd.. Nanoparticles with approx. 120 nm size were prepared by ion-ion interaction using chitosan and poly-gamma-glutamic acid (PGA), where PGA was modified with Folic acid (FA) via PEG linker and NODAGA chelator was conjugated to the chitosan.

AIMS: The aim of our work was the development of radiometal labeling- and quality control methods of functionalized nanoparticles, and supporting the development of new nanoparticle prototypes for in vivo imaging aplication.

RESULTS: Extensive study of labeling conditions with ^{68}Ga was performed in order to maximize radiolabeling yield and compare the properties of various nanoparticle preparations. The information, gained from the labeling experiments helped our partner to optimize the modification of the chitosan polymer used for nanoparticle synthesis and the conjugation protocol of the NODAGA chelator. Quantitative labeling could be reached in 15 minutes on room temperature at pH 5, adjusted with 10 µl 0.5M sodium-acetate buffer and 90 µl 0.05M sodium-hydroxide. Radiolabeling was monitored by radio TLC on ITLC-SG sheets using 0.1M citric acid as eluent. Purification of labelled nanoparticles on PD10 size exclusion resin slightly decreased the radioactivity concentration without any real advantage, thus it was omitted in animal experiments. Changes of nanoparticle size during la-

beling was monitored with Zeta Sizer Nano, and also used as an important imput for prototype development. Light scattering methods can not be used for size determination in plasma samples, thus we applied Wide Bore Hydrodynamic Chromatography to monitor size stability. The labelled nanoparticles appeared in the convection peak, well separated from small molecules, eluted in the diffusion peak.

CONCLUSIONS: ^{68}Ga labeling and folate targeting are used for the evaluation of in vivo stability and pharmacokinetics of the studied nanoparticles using PET/MR imaging in folate positive tumor bearing mice. After the selection of the optimal nanoparticle, RGD and NGR targeting will be applied for imaging neoangiogenesis in diabetic animal models.

O-22

Non-enzyme catalyzed metabolic transformations of xenobiotics

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BACKGROUND: A large body of evidence has been accumulating demonstrating importance of non-enzyme catalyzed metabolic transformations of xenobiotics. For example, inflammatory and other pathological processes are often accompanied by oxidative stress increasing the reactive oxygen and nitrogen radicals on the site of inflammation. Furthermore, endogenous thiols, e.g. reduced glutathione (GSH) possess an intrinsic reactivity with electrophilic xenobiotics and metabolites.

AIMS: To review and demonstrate importance of non-enzymatic oxidative metabolism of phenolic xenobiotics and reaction of reduced glutathione (GSH) with electrophilic xenobiotics. Demonstration of non-enzymatic metabolism of selenite, estrogens, salicylate and chalcones.

RESULTS: Experimental results demonstrated that non-enzymatic oxidation of phenolic compounds (e.g., estrogens and salicylate) plays important role in their metabolic feature and biological actions. They can act as radical scavengers protecting oxidative damage of sensitive endogenous compounds (e.g., lipids, nucleic acids) The nucleophilic antioxidant reduced glutathione (GSH) is also involved in a variety of non-enzyme catalyzed reactions. Such reactions can be manifested in both cytotoxic and cytoprotective effects.

CONCLUSIONS: Exponential results support that non-enzymatic transformation of xenobiotics can play important role in biological effects of the parent compounds.

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O-23

Gastrointestinal electromyographic signals during immobilization in rats: new possibility for the instrumental detection of stress

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BACKGROUND: Anxiety and stress frequently lead to functional gastrointestinal disorders. The existence of brain-gut axis is recently more than a simple hypothesis: the hormonal and neuronal interactions between the GI tract and the CNS have been approved (1). We have developed a method for the in vivo detection of GI tract activity applying smooth muscle electromyography (SMEMG) in rats (2). Our hypothesis is that the acute stress events should have a trace in the GI tract activity

AIMS: Our aim was to detect the GI tract activity during acute immobilization stress (30 min) in rats by SMEMG. Subcutaneous abdominal electrodes were implanted into rats. The magnitude of the activity was expressed as maximum of power spectrum density (PsDmax).

RESULTS: In stress, the PsDmax values of stomach, ileum and cecum were increased by 186, 144 and 148 %, respectively. The plasma corticosterone level was increased by 190%. Haloperidol (1 mg/kg) blocked both the stress-induced increase in PsDmax and in plasma corticosterone level, while diazepam (5 mg/kg) only reduced these parameters. Initial diazepam plasma level was 416 ng/ml, and it was reduced to 115 ng/ml at the end of stress period. Haloperidol was not detectable in plasma, but its high amount was found in brain before (299 ng/ml) and after (159 ng/ml) stress. The compounds were ineffective on the contractions of GI tract strips in vitro.

CONCLUSIONS: The acute stress-induced increase in corticosterone plasma level is reflected in the SMEMG signals of rat GI tract. Our method may open up a perspective for the instrumental detection of psychic stress and anxiety.

The work was supported by the project PIAC_13-1-2013-0201, National Research, Development and Innovation Office, Hungarian Government and by the EU-funded Hungarian grant EFOP-3.6.1-16-2016-00008.

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O-24

Effect of thyme, cinnamon and citronella essential oils in in vivo mouse lung inflammation model

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BACKGROUND: Respiratory tract diseases affect a large number of people in every age group worldwide. Unfortunately, the anti-inflammatory effect of essential oils (EOs) is weakly studied in well-designed respiratory tract inflammation in vivo models (1).

AIMS: The purpose of our study was to examine the chemical composition of thyme, cinnamon bark and citronella EOs with GC-MS. Moreover, our study aimed at the investigation of anti-inflammatory effect of these EOs in endotoxin-induced acute airway inflammation in vivo (mouse) model.

RESULTS: Thymol (46.1%), trans-cinnamaldehyde (45.9%) and citronellal (42.3%) were the main compounds in thyme, cinnamon bark and citronella EOs, respectively. In *in vivo* experiments, thyme oil could reduce the airway responsiveness in the treated groups compared to animals in the control groups, but it had no effect on other investigated parameters (e.g. inspiration and expiration time, relaxation time, etc.). Thyme EO significantly reduced neutrophil and macrophage MPO activity and also the extent of perivascular edema and perivascular/peribronchial inflammation. Inhalation of cinnamon bark oil also significantly reduced LPS-induced airway hyperresponsiveness, but it had no effect on neutrophil and macrophage MPO activity. It reduced the extent of perivascular edema, perivascular/peribronchial inflammation and the number of macrophages. Contrary, citronella EO significantly impaired the most of the respiratory parameters, and the MPO activity was also increased. The histopathological measurements also supported these findings.

CONCLUSIONS: Based on our results, the inhalation of thyme and cinnamon bark EOs decrease acute pneumonitis and airway hyperresponsiveness. Therefore, they can be considered as a potential treatment in such conditions. However, the use of citronella oil should be avoided, because it may cause irritation in the respiratory tract and exacerbates the inflammatory process. Further experiments are planned to measure the inflammatory cytokine profile and mechanism of action.

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O-25

Prevention of caspase activation by resveratrol in non-transformed cells

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BACKGROUND: Resveratrol is a natural compound with complex pharmacological activities. Among others its cytoprotective and cytotoxic effects are reported in the literature depending on factors such as its dose, duration of treatment and the model system.

AIMS: In this research our goal was to examine the effect of resveratrol on non-transformed cells as a potential cytoprotective agent against noxious insults.

RESULTS: In our model system resveratrol showed concentration dependent protective effect, as prevented caspase 3 activation in response to serum deprivation in primary fibroblasts. Its cytoprotective effect was further confirmed by the reduced release of lactate dehydrogenase (1).

The mechanism of effect was also studied. Among the major signaling pathways p38 stress kinase was found critical, as its inhibition eliminated the effect of resveratrol on caspase activation. Studying cellular stress revealed that resveratrol increased rather than reduced it. The compound augmented the generation of reactive oxygen species and caused depolarization of mitochondria.

As autophagy can protect damaged cells its role was also examined. Chloroquine, the inhibitor of late stage autophagy not only eliminated the protective effect of resveratrol, but turned it to deleterious. The improved autophagy flux in the presence of resveratrol was further confirmed by the reduced level of p62 protein a marker of autophagic degradation.

CONCLUSIONS: Our results suggest that resveratrol has a concentration dependent protective effect in non-transformed fibroblasts subjected to a noxious stimulus. The compound however acts by augmenting cellular stress that in turn can activate cytoprotective machineries, primarily autophagy. These results and hypothesis can help the understanding the contradictory effects of this popular natural compound.

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O-26

Effects of *Momordica charantia* (Bitter melon) on ischemic diabetic myocardium

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A rat model is here used to test a hypothesis that *Momordica charantia* (Bitter melon/BM) extract, favorably alters processes in cardiovascular tissue and systemically relevant to the pathophysiology of type 2 diabetes and related cardiovascular disease.

Body mass of both Lean and ZO rats and peripheral blood fasting glucose levels were unaffected by treatment. However, some BM treatment-related improvement was noted in postischemic cardiac functions when lean, BM-treated animals were compared with vehicle treated lean control rats. Treatment of lean, but not ZO rats significantly reduced the magnitude of infarcted zone in isolated hearts subjected to 30 minutes of ischemia and 2 hours of working mode perfusion (I/R). Immunohistochemical demonstration of caspase-3 expression by tissue of isolated hearts subjected to I/R, revealed significant correlation between BM treatment and reduced expression of this enzyme in hearts from both Lean and ZO animals. The hierarchy of caspase 3 expression from highest to lowest was as follows: ZO rats receiving mucin-water (5C) > ZO rats receiving BM extract (5D) > lean rats treated with mucin-water (5A) > Lean rats administered BM extract. Outcomes of analyses of peripheral blood content of cardiac-related analytes: with particular relevance to clinical application was a significant elevation in blood of ZO and ZO BM-treated, versus Lean rats of total cholesterol (high density lipoprotein HDL-c + low density lipoprotein LDL-c), with an inferred increase in HDL-c/LDL-c ratio. BM extract failed to positively affect T2DM- and cardiovascular- related outcomes at a level suggesting use as a standalone treatment. Nevertheless, the encouraging effects of BM in enhancement of cardiac function, suppression of post-ischemic/reperfused infarct zone extent and capacity to modulate serum cholesterol, will likely make it useful as an adjuvant therapy for management of T2DM and cardiovascular disease.

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O-27

Investigation of anti-inflammatory effect of sour cherry anthocyanins on Caco-2 inflammatory model

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BACKGROUND: The high biological value of anthocyanins is based on their antioxidant, anti-in-

flammatory and antiproliferative activities. High anthocyanin containing, thermostable sour cherry extract was produced at the University of Debrecen. The excellent properties of the sour cherry extract predict its expansive application.

AIMS: The aim of this study was to investigate of anti-inflammatory effect of sour cherry extract on inflammatory model of bowel diseases with Caco-2 intestinal epithelial cells. The examination of cytotoxicity of anthocyanin extract was performed by real-time cell analysis (RTCA). Monolayer permeability after pro-inflammatory cytokine (TNF-α, IL-1β) stimulation was tested by transepithelial electric resistance (TEER). IL-6, IL-8 production and activation of NF-κB pathway were also examined. The antioxidant capacity of anthocyanin extract was tested in Caco-2 cells by glutathione peroxidase (GPx) assay.

RESULTS: Decreased TEER values were measured after the pro-inflammatory cytokine treatment, however anthocyanin pre-treatment elevated the TEER values to the control level. Increased IL-6, IL-8 concentrations were detected in pro-inflammatory cytokine treated samples which was reduced in anthocyanin pre-treated samples. The NF-κB nuclear translocation indicated by high nucleus/cytoplasm intensity ratio was observed after pro-inflammatory cytokine treatment, which was significantly inhibited by anthocyanins. Reduced GPx activity were determined in anthocyanin pretreated Caco-2 cells after the cytokine treatment compared to stimulated cells.

CONCLUSIONS: Protective effect of sour cherry extracted anthocyanins on pro-inflammatory cytokine induced inflammatory activation in Caco-2 monolayers was investigated for the first time in this study. These results verify the effective anti-inflammatory and antioxidant capacity of sour cherry anthocyanins in Caco-2 cells.

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O-28

New drug delivery systems for the oral cavity and periodontal therapy

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In this lecture especially the drug delivery from periodontal pocket and new systems will be described after discussing the systemic and local drug delivery through oral mucosa and key considerations in the design and development of a drug delivery systems intended for use of oral cavity. Periodontal diseases are several pathological conditions in oral cavity and in recent years local drug delivery into the periodontal pocket has been investigated to overcome the disadvantages of systemic antimicrobial therapy.The periodontal pocket provides a natural reservoir, which is easily accessible for the insertion of local drug delivery devices. In my researches clindamycine phosphate (CDP) and metronidazole benzoate (MNZ) have been chosen as model drugs. CDP loaded microparticles were prepared by spray drying methodusing chitosan at one of my research and delayed drug release more than one week and minimum of 7 days' sustained antimicrobial activity could be obtained. It can be concluded that the easy scale up of spray drying method, the appropriate particle size, bioadhesive properties of chitosan were appropriate characteristics of these formulations for application into periodontal pocket (1). *In situ* implants containing MNZ for periodontal therapy were prepared at the other research by using PLGA 502H and 502S with different solvents. Using some adhesive polymers was novelty for *in situ* implants to maintain the longer retention time (2). MNZ loaded ethyl cellulose microspheres and NaCMC, Methocel K15M and K100M films were also studied. Than microsphere embedded adhesive films were prepared due to the difficulty of insertion of microspheres alone and burst release of drug could be decreased by that combination. Furthermore, CDP loaded chitosan films, CDP loaded chitosan-alginate complex films were studied. Our studies on periodontal nanoparticles are in progress.

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O-29

Design and characterization of mucoadhesive hydroxypropyl cellulose oral films

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BACKGROUND: Before their technological use, it is very important to determine the mechanical properties of mucoadhesive films because the free films are exposed to large mechanical stress during the preparation process, unpacking and sticking to the oral mucosa.

AIMS: Hydroxypropyl (HPC) cellulose free films were investigated as potential buccal drug delivery system. The effects of excipients on the polymer matrix were characterized in a wide range. *In vitro* mucoadhesion measurement method, equipment and software developed and optimized, and accelerated stability test was evaluated.

RESULTS: Tensile strength and PALS suggested that Xylitol (Xyl) forms hydrogen bonds. Thermal study suggested that excipients in low concentration incorporated into the system. Carbon dioxide, acetic acid and/or isopropyl alcohol formed during TG-MS study. The tested systems were thermally stable, below 100°C only water loss was detected. FTIR confirmed that both excipients incorporated to the polymer system via hydrogen bonds. Water uptake and migration were detected. XRPD also confirmed the incorporation of the excipients used, the system remained amorphous. Water uptake and migration were detected and confirmed via the changes of shape and angle halo of patterns. TGA confirmed the presence of bulk water. Tensile strength highlighted the softening behaviour of water and the over plasticization effect of it with Gly.

CONCLUSIONS: PALS demonstrated that Gly increases and Xyl decreases the free vacancies of the HPC films via moving the polymer chains. Tensile strength measurement and FTIR highlighted the so-called 'synergic' effect of Gly and Xyl used together. FTIR highlighted the potential novel application of Xyl as a plasticizer in pharmaceutical technology.

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O-30

Development of an orphan drug medicinal product for the treatment of maligant mesothelioma

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BACKGROUND: Mesothelioma is a rare lung malignancy characterized by a long latency period of 20-50 years after exposure to the main aetiology agent asbestos. In general, mesothelioma patients have three options: surgery, chemotherapy, and radiation therapy. Due to the high proportion of therapeutic failures in the treatment of MPM, and the high percentage with which recurrences manifest themselves, in particular after the postoperative chemotherapy, new approaches are needed (1).

AIMS: The aim of the research was to develop an implant for intrapleural or intraperitoneal application of cisplatin to be used during surgery for tumour resection to prevent local recurrence. The implant developed was a polymeric film of hyaluronic acid loaded with cisplatin (2).

RESULTS: Cisplatin films produced were characterized for physico-chemical, mechanical and drug release properties by means of various in vitro techniques. In addition, efficacy and toxicity studies were carried out in an orthotopic rat recurrence model of malignant pleural mesothelioma and in sheep respectively. Films produced were thin, flexible and assured a controlled release of cisplatin for up to 96 hours. These in vitro results were confirmed by a prolonged plasma levels of cisplatin in both animals models, as well as successful prevention in recidivation and better tolerability compared to intravenous or intrapleural administration of cisplatin.

CONCLUSIONS: The product developed was sccesfully submitted for orphan drug designation both by EMA and FDA. In addition, a clinical study protocol for a Phase I-II study has been developed in collaboration with the Scientific Advice Working Party of the CHMP of EMA.

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O-31

Development of a novel formulated, pulmonary microparticle (new generation DPI) containing antibiotic agent with improved aerosolization efficiency

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BACKGROUND: Inhaled antibiotics are of key importance in the treatment of cystic fibrosis-related lung diseases. Therefore the formulation of dry powder inhalers (DPIs) containing antibiotics could offer a potential way in drug therapy. The traditional carrier-based procedures (physical mixture of lactose and active agent) and a carrier-free (active agent with modified habit) alternatives can be applied to reach better aerosolization behaviours. The surface of the carrier and the habit of ciprofloxacin HCl (CIP) can also be affected by different technological methods.

AIMS: Our recent work introduced a novel combined formulation method, where the surface modification of the inhaled lactose and particle engineering of the drug were used before the blending. Therefore the effect of magnesium stearate and sodium stearate on the final formulation was investigated.

RESULTS: A constant concentration of magnesium stearate was used by interactive physical mixing (4h Turbula mixing) to cover the active places of the carrier. Sodium stearate (0-2 w/w%) was applied during the spray drying procedure to get suitable habit of the drug. A traditional formulation containing raw micronized CIP was prepared as a reference sample. The selected particle engineered formulation was then blended with modified lactose for 0.5 h. During a micrometrical (size, morphology, density) and structural (DSC, XRPD) characterization, spherical, ~ 2 μm sized particles of CIP with low density and amorphous characters were detected. *In vitro* aerodynamic measurements revealed a high lung deposition (more than 70%) of the products. By applying a newly determined *in silico* model, the suitable inhalation manoeuvre was also predicted.

CONCLUSIONS: A new generation DPI formulation of CIP was prepared by a first applied combined method, which could help to improve the efficacy of pulmonary therapies.

This project was supported by GINOP-2.3.2- 15-2016-00036 program and ÚNKP-17-4-III-SZTE-3 New National Excellence Program of the Ministry of Human Capacities..

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O-32

Dissolution extent decrease of amorphous drug due to magnesium stearate induced crystallization

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BACKGROUND: By the aid of amorphous solid dispersions, extremely poor dissolutions of lypophilic drugs can be enhanced, often to 100%. However, downstream processing (and/or storage) may deteriorate this advantegous dissolution by crystallization or in other, yet unknown way. It is important to avoid these phenomena to maximize dissolution, and possibly bioavailability.

AIMS: Our aim was to reveal how magnesium stearate (MgSt) lowers dissolution extent of perfectly amorphous itraconazole in course of in vitro dissolution test. Furthermore, possible ways are searched to eliminate this issue.

RESULTS: Based on the experiments, dissolution extent of itraconazole (incorporated in amorphous solid dispersion with PVPVA64) from tablet formulation depends on the temperature and MgSt content. MgSt can be dissolved in acidic dissolution medium where it forms stearic acid. NMR examination and elemental analysis showed that itraconazole, a weak base, formed an insoluble salt with stearic acid (itraconazole-stearate). This previously unreported phenomenon can be avoided by the application of other lubricant (sodium stearyl fumarate) or polymer matrix in the dispersion (HPMC).

CONCLUSIONS: MgSt can deteriorate the dissolution of amorphous itraconazole through a salt formation phenomenon. It is yet to be evaluated if this affect other amorphous, basic drugs or it is specific for itraconazole.

O-33

Behaviour of medicated inks on porous substrates – The effect of viscosity and surface tension on printing parameters

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BACKGROUND: 2D and 3D printing methods are of emerging interest in the pharmaceutical industry, since their offer enormous advantages from the aspect of dosing accuracy, modification of the drug release kinetic and personalized medicine [1]. Genina et al. revealed that the ink parameters (e.g spreading on non-porous substrates) may influence both printing accuracy and the behaviour and stability of the printed drugs [2].

AIMS: Current project is focusing on the investigation how the physicochemical characteristic of the applied medicated ink influence the printing and dosing accuracy, the penetration into and the distribution inside a porous substrate.

RESULTS: PVP K25 and Polysorbate 80 was used for setting of the viscosity and surface tension of the ink according to 3^2 full factorial design, which contained brilliant blue dye as model material to help to follow the ink distribution of the texture of carrier matrix. 13 mm in diameter tablets with different porosity were compressed from Pearlitol SD200 (Roquette, France) lubricated with 1% of magnesium stearate using a hydraulic press (Specac, UK) and 2, 3, 4 and 5 tons compression force. The surface tension and spreading parameters of the ink on the substrate surface was tested with an optical contact angle tester (OCA20, Dataphysics, Germany). The printing experiments were conducted with a self-developed printing apparatus. The results revealed that the viscosity plays considerable higher role in the ink behaviour than surface tension, low viscosity promotes the ink penetration into the substrates which acts positively on the printing speed, but negatively affects the printing pattern especially in highly porous substrates.

CONCLUSIONS: There are complex interrelations between ink parameters and properties of porous substrates, which allows multiple ways for tailoring individualized delivery systems.

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O-34

Challenges in equilibrium solubility measurements: poor solubility, low dissolution rate, low wettability

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BACKGROUND: Various methods are available for the measurement of equilibrium solubility but the saturation shake-flask (SSF) technique has still remained the "gold standard" approach [1]. It is a very simple method, however to obtain high-quality data one has to pay attention on several critical experimental conditions among them on the incubation time. Substances which dissolve very slowly generally need long incubation times (days or weeks) to reach equilibrium. However, long times may pose several problems. In 1979, the Facilitated Dissolution Method (FDM) was proposed to dramatically reduce incubation time [2]. It employs a small volume of water-immiscible organic solvent to partly solubilize the sample and thereby increase the surface area available for dissolution. The method has been used only rarely and never validated.

AIMS: The aim of the present study was to conduct a systematic validation of FDM using progesterone as model compound. Further goal was to identify a standardized protocol of this method and prove its applicability in case of compounds with slow dissolution rate.

RESULTS: Using progesterone as a benchmark, the conditions of the FDM were optimized by changing several experimental factors. Second, four drugs known to have low dissolution rate were studied: dexamethasone, digoxin, haloperidol , and cosalane. The time dependence of solubility equlibrium was measured by SSF and the results were compared with those obtained by FDM.

CONCLUSIONS: Our study supports the validity of Higuchi's method. Here we propose a standardized protocol for the FDM, where 1% v/v of organic solvent is used. In the presentation other factors affecting the accuracy of SSF method are also surveyed and recommendations for the best practice are committed.

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O-35

Targeted delivery of solid and vesicular nanoparticles across the blood-brain barrier

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BACKGROUND: Therapy of neurological diseases is difficult, due to the restricted drug delivery across the blood-brain barrier (BBB). Nanoparticles targeting transporters of the BBB are promising candidates to increase the CNS penetration of drugs.

AIMS: To compare different ligands of BBB transporters as targeting molecules for solid and vesicular nanoparticles.

RESULTS: Fluorescent polystyrene nanoparticles were derivatized with biotin and biotinylated glutathione. Niosomes were derivatized with glucopyranose, alanin and glutathione, and loaded with albumin-Evans blue complex. Nanoparticles did not change the viability of brain endothelial cultures. Biotin and glutathione increased the uptake of solid nanoparticles by brain endothelial cells in a time-dependent way. The cellular uptake was verified by confocal microscopy. Targeting ligands also increased the uptake of the cargo in the cells which was temperature dependent and could be decreased with a metabolic inhibitor. The permeability of both the solid nanoparticles and the cargo across brain endothelial monolayers was increased by targeting vectors. Glutathione-labeled solid nanoparticles crossed the BBB model better than the biotin-targeted ones. Treatment with niosomes increased plasma membrane fluidity in endothelial cells suggesting fusion with the cell membranes.

CONCLUSIONS: Biotin as a targeting ligand increases the uptake and the transfer of solid nanoparticles across brain endothelial cells. Glutathione is effective to increase nanoparticle permeability through BBB models. Our data indicate that nutrient transporter ligands can potentially be exploited for CNS targeting of nanoparticles.

O-36

Bile salt transport profiling of hepatic transporters

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Transporters have important endobiotics among their substrates. Drug-mediated inhibition of transporters may alter homeostasis of transporters and, thus, precipitate toxicity or adverse reactions.

Bile acids/salts are among the first chemical class of endobiotics that has been associated with a pathological condition such as cholestasis. A genetic impairment of function of the canalicular bile salt efflux pump (BSEP/ABCB11) in humans leads to progressive familial intrahepatic cholestasis type II (PFIC II). It has been long recognized that drug mediated inhibition of BSEP may also lead to cholestasis. Other canalicular efflux pumps such as multidrug resistance associated protein 2 (MRP2/ABCC2) has also been implicated in bile salt transport. More recently influx transporters, most importantly sodium-taurocholate co-transporting polypeptide (NTCP/SLC10A1) and organic anion transporting polypeptide 1B1 (OATP1B1/SLCO1B1) have been shown to play important roles in hepatic uptake of bile salts. If canalicular efflux is blocked sinusoidal efflux transporters MRP3/ABCC3 and MRP4/ABCC4 get induced and efflux bile salts into the blood.

Taurocholate is the prototype bile salt most often used to characterize these bile salt transporter functions. Taurocholate is a monovalent amidated bile salt and even among amidated bile salts it is not the most abundant bile salt in healthy humans. Moreover, it is a relatively hydrophilic trihydroxy bile salt and, thus less toxic.

We have profiled bile acid/salt transport of BSEP, MRP2-4, NTCP and OATP1B1 using different classes of bile acids/salts such as a bile acid, monovalent bile salt, sulfated bile acid and divalent bile salt. Selectivity of bile salt transport by these transporters will be discussed.

Financial support: the work was supported by IMI consortium MIP-DILI.

O-37

The role of biocompatibility investigations in pharmaceutical technological research

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BACKGROUND: BACKGROUND: Pharmaceutical excipients are widely used for the preparation of different dosage forms. The simultaneous presence of these materials can often result in drug-excipient or excipient-excipient interactions, which can possible be advantageous (e.g. solubility enhancement) or even harmful (e.g. allergic reaction). Thus, the profound safety screening of excipients (such as CDs, preservatives, tensides etc.) are always indispensable, including their pharmacokinetic and toxicological profile (1). Different in *vitro cell culture* biocompatibility tests were developed to simulate and predict biological reactions to materials when placed into or on tissues in the body (2).

AIMS: Our objective was to investigate various group of pharmaceutical excipients using different cytotoxicity methods on Caco-2 and HeLa cell lines. Further aim was to prove the applicability of MTT cell viability, LDH and hemolysis tests in the routine toxicological investigation and to determine relationship between their chemical structures and cytotoxicity profiles.

RESULTS: Nine α-CD derivatives on Caco-2 cell lines and on human erythrocytes were investigated. Chemical modification on the free hydroxyl groups have a definite impact on toxicity. Toxicity depends on the number of building units. The rate of toxicity depends on the exposition time. The intensity of CD cytotoxicity varies on different cell types. We also tested tensides with various chemical structures. There were significant differences in the cytotoxic properties of surfactants in a concentration-dependent manner. Polyoxyethylene glycol based tensides are more toxic surfactants than propylene glycol esters. If we combined surface active agents with preservatives and/or with polymers, in some cases polymers showed a cell-protective effect, but tensides can decrease the biocompatibility of preservatives and polymers in liquid pharmaceutical dosage forms.

CONCLUSIONS: It can be concluded that in vitro biocompatibility test can predict the tolerability of pharmaceutical excipients and may ensure useful information about the interactions of excipients.

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O-38

Examination of pharmacokinetic properties of fluorescently labelled hydroxypropyl-beta-cyclodextrin

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BACKGROUND: A new renaissance started in the research and application of cyclodextrins a few years ago. The number of novel derivatives are increasing and new applications has been appeared. Fluorescent cyclodextrin derivatives are new tools in cyclodextrin research. By the help of these molecules the cellular interactions of cyclodextrins can be visualized and their biological activity can be monitored by fluorescent techniques.

AIMS: The aim of our study was to test the pharmacokinetic properties of fluorescein-isothiocyanate labelled hydroxypropyl-beta-cyclodextrin (FITC-HPBCD) and to study its internalization on different cell lines.

RESULTS: FITC-HPBCD pharmacokinetic analysis was carried out on BALB/c mice. The blood concentration decreased rapidly after i.v. administration in the function of time, showing fast elimination. Accumulation of FITC-HPBCD in different organs could not be measured in tissue homogenates at the end of the experiment. In vivo imaging technique confirmed fast elimination. The cellular internalization of FITC-HPBCD was detected by fluorescent microscopy on Caco-2, HaCaT and HUVEC cells. Endocytosis of FITC-HPBCD in the primary human endothelial cell line, HUVEC can

explain the first step of tissue distribution of cyclodextrins.

CONCLUSIONS: The in vivo behaviour of fluorescent cyclodextrins can be easily examined by fluorescent techniques, thus these derivatives are suitable for pharmacokinetic measurements. Our data are in accordance with earlier results and reveals that HPBCD can be internalized by several cell types.

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O-39

Diarylheptanoid composition of several European Betulaceae species

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BACKGROUND: Diarylheptanoids are a group of phenolics bearing a 1,7-diphenylheptane skeleton. Due to the anti-inflammatory and antitumor activities of diarylheptanoids, the search for new plant sources is gaining significance.

AIMS: The aim of our work was to study and compare the distribution of diarylheptanoids in several species of the Betulaceae family.

RESULTS: *Alnus glutinosa* (L.) Gaertn., *Alnus cordata* (Loisel.) Duby, *Alnus incana* (L.) Moench, and *Carpinus betulus* L. (Betulaceae) were evaluated. Leaf, bark, involucre and catkin samples, additionally, *in vitro* callus cultures of *A. glutinosa* were investigated by HPLC-DAD-ESI-MS/MS. For the separation of the constituents RP-HPLC methods using linear gradient elution with acetic acid in water (0.2%, v/v) and methanol as eluents were applied. Oregonin [1,7-bis-(3,4-dihydroxyphenyl) heptan-3-one-5-*O*-β-D-xylopiranoside] and hirsutenone [1,7-bis-(3,4-dihydroxyphenyl)-4-hepten-3-one] were detected as the main diarylheptanoids for the *Alnus* samples, similarly to the *Corylus* species investigated in our previous works [1-2]. In *C. betulus* hexosides and glucuronides of linear-type diarylheptanoids, as well as macrocyclic constituents were detected.

CONCLUSIONS: Diarylheptanoid composition of leaves, involucres and catkins of the above mentioned *Alnus* and *Carpinus* species has been studied for the first time. Our further aim is the isolation and structural identification of the detected compounds, in order to investigate their *in vitro* cytotoxic activity.

The financial support from NKFIH K 120342 is highly appreciated.

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O-40

Melt electrospinning of fibers from the molten mixtures of a carrier material and drug

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Electrospinning is a one-step continuous process in which an electrical field is used to "draw very fine fibers from a viscous solution, suspension, or molten material. Electrospinning has been used for fabrication of medicinal scaffoldings and amorphous solid dispersions of carrier polymers and active pharmaceutical ingredients [1]. The drawback of electrospinning from the polymeric solvent systems is that organic solvents used are usually toxic or harmful. Melt electrospinning can directly produce polymer nanofibers at elevated temperatures, thus avoiding the use of expensive and hazardous solvents. However, only few studies have used this technique to date [2].

The aim of the present study was to develop melt electrospinning methods applicable for preparing microfibers composing of a binary or ternary mixture of drug and polymer(s) or sugar(s). The ultimate goal was to improve the overall solubility and dissolution rate of a poorly water-soluble drug (indomethacin as a model drug). It is expected that the increased surface area of the fibers and rendering the material amorphous will have a positive effect on the dissolution characteristics of drug. The chemical stability of the materials during melt electrospinning, molecular interactions and solid-state changes were studied using a solid-state nuclear magnetic resonance spectroscopy (NMR), thermogravimetric analysis, differential scanning calorimetry (DSC), Raman spectroscopy and Fourier Transform infrared spectroscopy

(FTIR). The morphology of the fibers was investigated with optical and scanning electron microscopy (SEM).

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O-41

Development of hollow nanostructures for magnetically-assisted drug delivery

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Inorganic nanobiomaterials generally exert higher thermal and chemical stability as well as better resistance to physiological conditions compared to the organic counterparts, thus nowadays they attract special attention in biomedical field. Among them magneto-responsive materials based on superparamagnetic iron oxide nanocrystals (SPIONs) are especially interesting, since they enable magnetic drug targeting i.e. the remote control over the distribution and accumulation of the nanocarrier in the body [1]. However, preparation of effective and robust magnetically responsive nanocarriers still represents a great scientific challenge, due to physical limit of individual SPIONs, namely the too small magnetic force acting on individual nanocrystals exposed to magnetic field gradient, resulting in their ineffective spatial guidance. The solution to this shortcoming could be assembly of numerous individual SPIONs into superparamagnetic nanoparticle clusters, which exert good magnetic responsiveness, due to the increased volume of magnetic phase. In well-defined magnetic fields the clusters can form various hierarchical nanostructures (i.e. nanobundles, nanochains), having a great potential for the preparation of innovative magneto-responsive nanodelivery systems [2].

The presentation will briefly describe the synthesis of well-defined magnetic nanoparticle clusters and their assembly in hierarchical nanostructures. Then the development of magneto-responsive delivery system based on such clusters will be presented. The special attention will be paid to the method of drug loading, drug release studies and *in vitro* biocompatibility evaluation.

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O-42

Development and characterisation of a gel formulation containing ibuprofen-loaded nanostructured lipid carriers

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BACKGROUND: Ibuprofen is a potent NSAID used for treating different forms of pain. Its low water-solubility and low bioavailability are great challenge in the development of dermal preparations.1 Nanostructured lipid carriers (NLCs) can overcome this problem.2 The dermal use of NLC systems offer many advantages: physical stability of the formulations, increased chemical stability of the incorporated drugs, improved skin bioavailability, film formation on the skin accompanied with controlled occlusion, skin hydration.1,2

AIMS: The aim of this work was to develop ibuprofen-loaded NLC (IBU-NLC), to achieve increased transdermal API penetration. The optimized formulation was incorporated in a gel; *ex vivo* and *in vivo* penetrations were compared to a conventional ibuprofen formulation.

RESULTS: Characterization of the IBU-NLC dispersion proved appropriate size range and morphology. XRD measurements and the high entrapment efficiency (98.51%) both confirmed the presence of IBU as a molecular dispersion in the lipid matrix of the final formulation. The homogeneous distribution of IBU in the lipid matrix and the weak interactions between the drug and the excipients predicted rapid drug liberation. The *ex vivo*, *in vivo* penetration studies demonstrated significantly higher drug permeation from the IBU-NLC compared to the reference formulation.

CONCLUSIONS: It can be concluded that the IBU-NLC gel is of great potential to increase drug permeation through the skin and enhance the efficacy of the treatment for osteoarthritis and other musculoskeletal inflammations compared to a conventionally prepared ibuprofen gel.

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O-43

Formulation and characterisation of nanofibrillar cellulose consisting nanofibrous mats intended for novel wound dressings

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BACKGROUND: Cellulose nanofibrils, also termed as nanofibrillar cellulose (CNF), have several unique material properties for excipient use in both immediate-release and controlled-release dosage forms. CNF is non-toxic, has high surface area and excellent mechanical strength that could be used to improve the mechanical properties of the dosage forms (1). CNF absorbs a lot of water and readily forms a gel which makes it a suitable candidate to be used also as a wound protective material (2).

AIMS: The aim of the present study was to investigate the electrospinning (ES) of CNF and to find optimal process conditions and solvent systems for fabricating CNF-based nanofibrous mats. The fiber size, size distribution, surface morphology, and physical solid-state properties of the nanofibers were studied.

RESULTS: The formulations consisting CNF and a water-soluble polymer (polyethylene oxide, PEO) in various concentrations were tested. The process parameters of ES were varied to improve the processability of the nanofibers. It was found that the 1:1 ratio of CNF (0.135 w/v% aqueous dispersion) and PEO (8 w/v%) solution in ES produced the nanofibers with an uniform structure. The mean diameter of the fibers was less than 200 nm, and the fiber diameter was dependent on the voltage used. When CNF was added to the PEO solution, the diameter of the fibers decreased compared to that obtained with the pure PEO fibers. Higher concentration of CNF impaired the ES process, and consequently, several beads were detected on the nanofibrous mats.

CONCLUSIONS: CNF can be successfully electrospun with PEO. Further studies will reveal the mechanical properties, stability, swelling and degradation behavior of the present nanofibers.

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O-44

In vitro investigation of antimicrobial electrospun wound dressings based on chloramphenicol and biodegradable polymers

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BACKGROUND: Infection and biofilm formation are increasingly associated with non-healing and chronic wounds [1]. In order to develop novel wound dressings/drug delivery systems to tackle with this problem and understand their potential effectiveness, full physicochemical, mechanical and biopharmaceutical characterization needs to be performed in addition to the antibacterial and cytotoxicity studies.

AIMS: To develop chloramphenicol-loaded electrospun dressings and investigate properties important for the successful treatment of wound infections.

RESULTS: Chloramphenicol-loaded matrices using different carrier polymers were developed and characterized morphologically (scanning electron microscopy, atomic force microscopy, mercury intrusion porosimetry and BET analysis), physicochemically (XRD, FT-IR, DSC), and biopharmaceutically (drug release). Also mechanical and swelling properties of the matrices and physical stability in biorelevant liquid medium were studied. Antibacterial properties of the dressings were revealed and compared using disc diffusion assays and also biofilm studies in a novel artificial wound model. Safety of the matrices on eucaryotic cells was confirmed with cytotoxicity testing on NIH 3T3 fibroblasts.

CONCLUSIONS: Two potential wound dressings with different structural, physicochemical and mechanical characteristics as well as different drug release behavior were developed. Both were biocompatible and had adequate antibacterial activity, but differed greatly in drug release profiles and swelling properties. It was possible to investigate and confirm the antibiofilm properties of the dressings using an artificial wound model.

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O-45

A science based approach for Topical drug Classification System (TCS)

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Determining the bioequivalence of topical drug products is challenging, complicated and also cumbersome. We have developed a Classification system for Topical Drug Products, TCS, based on established scientific principles specifically developed for semisolid topical drug products (SUPAC-SS) and is combined with the in vitro release (IVR) of the drug product. The TCS classification is similar to the well-established Biopharmaceutics Classification System (BCS) for immediate release oral drug products. TCS considers the qualitative (Q1) and quantitative (Q2) composition of inactive ingredients and microstructure arrangement of topical semisolid products. The IVR reflects the combined effects of several physico-chemical characteristics, particle or droplet size, viscosity, the microstructure arrangement of the matter (Q3) and the state of aggregation of the dosage form. Based on composition (Q1 and Q2) and IVR similarity (Q3), the topical drug products are classified as TCS class 1, 2, 3 and 4. Under the proposed classification - only TCS class 1 and TCS class 3 drug products are eligible for biowaiver; TCS class 2 and TCS class 4, are not eligible for biowaiver and will require appropriate *in vivo* BE studies for drug approval. The TCS simplifies the regulatory requirements and reduces the regulatory burden, and maintains the drug product quality. It will also make the drug products more affordable to consumers.

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O-46

Some bioequivalent (BE) modified-release (MR) formulations with multiphasic concentration profiles are not interchangeable

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BACKGROUND: It is widely assumed that if the bioequivalence of two drug products is approved then (provided that they are also pharmaceutically equivalent) they are therapeutically equivalent and, consequently, interchangeable. It has been shown in several cases that these assumptions have not been satisfied.

AIMS: To demonstrate that MR, multiphasic methylphenidate (MPH) formulations are not interchangeable even when they have been declared to be BE.

RESULTS: The time profiles of concentrations in several MR, multiphasic MPH preparations are very different even though they have similar maxima and areas under the curve. Consequently, they have differing pharmacokinetic features even though they satisfy the regulatory criteria for bioequivalence.

CONCLUSIONS: The differing characteristics of apparently BE formulations raise doubts about their interchangeability. Similar questions persist also for other classes of drug products.

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O-47

Navigating the regulatory information maze

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BACKGROUND: In the pharmaceutical industry as well as for health care professionals and patients it is important to identify the information and documents relevant to their everyday work, activities, life, etc.

AIMS: Aim of the presentation is to introduce what type of information and documents are publicly available and how to search for them.

CONCLUSIONS: The pharmaceutical regulatory environment is continuously evolving and has become very complex by today. Transparency is an important feature of this environment that has reached a never-before level in the recent past. Medicines agencies are public authorities and are obliged to be open as for their operations as well as for information on clinical trials, medicinal products and for access to documents. The benefit of the transparent operation is, but not limited to, strengthening the scientific, technical and administrative competencies in the pharmaceutical environment, the effective information sharing and

collaboration of the stakeholders. The European Union law sets the minimum level of transparency that the European Medicines Agency must apply. However, in many areas, the Agency has decided to go beyond what the law requires providing as much information publicly available as possible. The presentation identifies the type and source of information that the Agency releases either mandatorily or proactively and how the public can navigate in the enormous amount of information. In addition the presentation summarises where health care professionals and patients can source their information from.

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O-48

Long-term dissolution method for poor water-soluble parenteral suspension

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BACKGROUND: Sustained release (SR) injectable suspensions are already used in clinical practice because they have advantages: lower frequency of administration, blood levels remain within therapeutic range, greater effectiveness and reduced side effects. Such suspensions may be administered in the form of a low soluble drug, but the release time of such medication is dependent on the particle size and the specific surface area.

AIMS: In drug development, it is very important to have reliable method how to evaluate drug dissolution profile in *in vitro* conditions before clinical trials on animals and humans. In the case of low soluble drug, common dissolution tests are not applicable because of drug insolubility. Therefore, we have developed a new *in vitro* dissolution method to evaluate the dissolution profile of such medication. Moreover, this method is also useful for the development of generic drugs, to compare their dissolution profile to those of the reference. Enzymatic dissolution tests of our drug suspensions were conducted with various PSD by the enzyme serine esterase.

RESULTS: For each sample taken at various time intervals, the increase of API concentration and reduction of PSD of the suspension were evaluated using HPLC and laser diffraction, respectively. Based on the results of this work, the rate of kinetic release was found to correlate directly with an increase in the specific surface area of the particles in the suspensions. The proposed in vitro method is used to predict the pharmacokinetics of the medication under *in vivo* conditions.

CONCLUSIONS: Thus, it can serve as a cheaper and faster alternative for bioequivalence studies (BES) on animals used in generic drug development. However, further validation studies will be required to relate our method quantitatively to real *in vivo* conditions.

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O-49

New advances in continuous pharmaceutical technology

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BACKGROUND: Continuous manufacturing of pharmaceuticals, being especially suitable for instantaneous quality monitoring and control, allows sudden reaction to market changes and cut development and upscaling costs. The choice of available scalable integrated continuous technologies is, however, limited.

AIMS: A complex research program aiming to widen the choice of techniques applicable for continuous formation of amorphous solid dispersion (ASD) was started recently. The design of each step considered the application of process analytical technology (PAT) tools and feedback control in order to ensure output of stabile quality through flexible and robust production.

RESULTS: Extrusion process being able to operate under wet, melt or supercritical (Sc) circumstances was developed and evaluated using various polymers such as PVPVA64, Soluplus and others. The role of parameters and components on the

amprphicity, homogeneity and dissolution characteristics was evaluated. Sc-extrusion allowed milder processing parameters and resulted in fast dissolution. Nanofiber production with enhanced productivity could be developed applying various techniques such as high speed (HSES), alternating current (ACES), fibre blowing and melt blowing. Further improvement in dissolution rate of drugs (of BCS II. type) could be achieved in all cases. Considerable challenge was to match appropriate downstream steps to these continuous production lines and combine them with in-line Raman sensor supporting real time release. Novel feedback control was developed for powder blending and drug crystallization using UV and/or Raman sensors. These steps were integrated with drug synthesis in flow reactor resulting in end to end continuous pharmaceutical technology.

CONCLUSIONS: Development of new integrated continuous technology with in line control resulted in several advantages. Higher bioavailability was predicted for the formed ASDs of enhanced dissolution. The developed spectroscopy-based process control with well-designed chemometric techniques allowed adjusting the control strategy and process parameters to the required stable product quality. Real time release helps to avoid production losses resulting in more economic and safe manufacturing of pharmaceuticals.

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O-50

Application of the Quality by Design methodology in the R&D phase: implementation of „co-creation" with regulatory agencies, pharmaceutical industry partners and patients

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BACKGROUND: Quality by Design (QbD) is a concept introduced by Dr. Joseph M. Juran, emphasizing the design of quality into products and services (1). This QbD approach is a risk and knowledge based holistic and systematic way of pharmaceutical developments as well, and it is highly recommended by the regulatory authorities. The elements of the QbD methodology are described in the ICH Q8 (R2) international guideline dedicated for the industry (2).

AIMS: The aim of this work was to collect all relevant stakeholders and evaluate their quality expectations concerning the active agent, dosage form composition and manufacturing process; as well as the choice of the administration route. This work was followed by creating and pilot testing of a modified flow chart of Quality by Design methodology together with a guideline for formulators in case of different dosage forms and administration routes.

RESULTS: Based on the preliminary data, we experience (a) an increased need for the evaluation of the „unmet clinical needs", (b) special focus and implementation of the preformulation study design based on the inputs of regulatory agencies and also the feedback from industrial partners of the pharma sector, and (c) put more emphasis on control strategy.

CONCLUSIONS: Based on our research experiences in case of topically, nasally and pulmonary administered different dosage forms and different carrier systems; the "R& D - QbD" was found to be a useful tool – set to formulate products for quicker transfer to manufacturing and marketing authorization, meeting the requirements of the defined key stakeholders.

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O-51

Optimization of flurbiprofen nanosuspensions: The QbD approach

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BACKGROUND: Flurbiprofen (FB) is the one of non-steroidal anti-inflammatory drugs which has low water solubility. Nanosuspensions (NS) are promising drug delivery systems consist of pure solid drug particles mainly. Due to their mean particle size below 1000 nm, they increase solubility, dissolution and bioavalibility of poorly soluble

drugs. Quality by design (QbD) is a systematic approach to predict quality of NS with desired and predetermined parameters **(1).**

AIMS: The objective of this study was to prepare flurbiprofen nanosuspensions (FBNS) using DoE with 2^3 full factorial design. FBNS were produced using microfluidization method and stabilized with Plantacare 2000 (PL). Effect of critical formulation attributes (CFAs), critical process parameters (CPPs) and their interactions were determined.

RESULTS: The particle size (PS), polydispersity index (PDI) and zeta potential (ZP) were found 630±10 nm, 0.210±0.032 and -34.7±0.586 mV, respectively as a function of 2 level of FB:PL ratio (A) (1:1, 1:2), homogenization pressure (B) (20000-30000 psi) and homogenization cycles (C) (10-30 cycle). All parameters were evaluated using univariate ANOVA at α=0.05 as the minimum level of significance. The 3-way interaction between independent variables was found to be insignificant ($p>0.05$). Therefore, the 2-way interactions and main effect of independent variables were evaluated. All main effects and 2-way interactions between A*B and A*C were found to be efficient on PS and ZP values. FB:PL ratio and 2-way interaction between B*C were efficient according to PDI. The influence of CFAs and CPPs for the optimization of FBNS was determined using QbD approach successfully. The optimum formulation and process parameters were found as 1:1 FB:PL ratio, 26000 psi homogenization pressure and 30 homogenization cycle.

CONCLUSION: This study demonstrated the usefulness of QbD approach using DoE to understand the optimum homogenization process parameters of FBNS.

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O-52

Application of flow techniques as a research tool in pharmaceutical area

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BACKGROUND: Various flow techniques (FIA, SIA, SIC, MSA, MSC, LOV, etc.) are already well established analytical techniques, which are characterised by simplicity of fundamental principles, inexpensive instrumentation, automated sampling and analytical procedures, low sample consumption and short analysis time. Flow methods offer several advantages, mainly the instrumental set-up is very flexible and the hydrodynamic variables are easily controlled with high efficiency, thus flow methods are becoming a convenient research tool in pharmaceutical area.

AIMS: Automated flow analytical methods are recently more and more used as a simple sample preparation step (automation of various extraction techniques) or for long-term monitoring. Flow techniques can automate the analysis and control long-term measurements such as dissolution, liberation or permeation tests of pharmaceuticals.

RESULTS: A fully automated system based on the SIA technique connected to the Franz cell (enables to mimic real conditions in the human skin and penetration of the drug through the dermal barrier) can easily monitor on-line the release rate of pharmaceuticals [1]. Sequential injection chromatography (SIC) was introduced firstly in 2003 [2] as an alternative of high performance liquid chromatography (HPLC) for fast analysis of relatively simple samples. Implementation of short monolithic chromatographic column into SIA has expanded also to analysis of pharmaceutics.

CONCLUSIONS: An overview of the use of flow techniques as a research tool in pharmaceutical area either as a simple technique for automation and sample preparation or for monitoring of pharmaceutically important procedures or finally as a simple alternative for separation procedures will be discussed. The authors gratefully acknowledge the financial support of Grant Agency of the Czech Republic (GAČR), project No. 15-10781S.

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O-53

Application of simultaneous dissolution-absorption apparatus for screening formulations before bioequivalence studies

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BACKGROUND: For generic drug development traditional dissolution tests have been used in the pharmaceutical industry to compare performance

of different drug product formulations before conducting bioequivalence studies, even though the in vivo predictive power of these tests are questionable.1 Namely, when a poorly water-soluble API is formulated to enhance its dissolution, additives have an effect not only on dissolution, but also on flux through the membrane.[2]

AIMS: The aim of this study was to represent that a simultaneous dissolution-absorption test can be used as a predictive tool before bioequivalence studies are conducted.

RESULTS: Telmisartan tablets were tested using MacroFLUX™: Receiver chamber integrated with permeation membrane, overhead stirrer and UV probe was inserted in the standard 900 mL vessel of USP II apparatus. The dissolution and flux results of the brand name (Micardis) and generic (Actavis) Telmisartan 40 mg tablets were compared. Actavis showed a slower release kinetics than Micardis, though reached the same maximum concentration after 110 min. The flux from the generic product was found to be 0.240 ± 0.011 μg/(cm²min), which is only 71% of the flux of the brand name (0.337 ± 0.028 μg/(cm²min)). This *in vitro* result showed excellent correlation with the *in vivo* data from bioequivalence studies, where the appearence rate or the drug in blood from Actavis was 72 % of the rate from Micardis.

CONCLUSIONS: The *in vivo* predictive power of the simultaneous dissolution-absorption test was demonstrated by comparing the *in vitro* fluxes to *in vivo* rate of appearance in blood of brand name and generic formulation of telmisartan.

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O-54

Translation of clinical pharmacy research into practice: a Slovenian case

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Clinical pharmacists in Slovenia have succeeded in the development and application of all relevant research methodologies to maximize the clinical effect of medicines, minimize the risk of treatment-induced adverse events and minimize the expenditures for drug treatments.

On the basis of numerous original research articles published in leading journals at the area of outcomes research (1,2), two types of clinical pharmacy services are currently in the process of implementation in community care and in hospitals.

In community care *Medication use review* is offered in community pharmacies, while in community health centres and in nursing homes a practice of pharmacist consultant service is available as *Advanced medication review*. *Medication use review* includes medication history and patient information, whereas *Advanced medication review* is based on medication history, patient information and clinical information, which is obtained from patient's medical records. The practice of pharmacist consultant is started by a general practitioner who identifies either patients with potential drug adverse reactions or patients with potential drug-drug interactions in the case of polypharmacotherapy. These patients and their medical records are referred to the pharmacist. The pharmacist's report is sent back to the general practitioner who optimizes the pharmacotherapy in accordance with the patients. The acceptance rate of pharmacist's proposals is approximately 70%. The practice of pharmacist consultant is financed as the regular health program by the Health Insurance Institute of Slovenia since 2016.

A full scale model of clinical pharmacy activities **in clinics and hospitals** has been introduced as early as in 2007. They are performed in the wards at the patients' bedside and in the hospital management system. Clinical pharmacists participate in medical rounds, perform *Advanced medication review*, implement Medication reconciliation process, perform Therapeutic drug monitoring activities and prepare Drug formularies. Additionally, they participate in hospital committees for drugs, antibiotics and hospital infections, take an active role in creating pharmacotherapeutic guidelines and start setting up clinical pharmacy departments.

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O-55

Cariprazine, a new generation atypical antipsychotics: Clinical overview

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BACKGROUND: Schizophrenia is a chronic and

disabling psychiatric disease characterized by 3 core symptom domains: positive symptoms, negative symptoms, and cognitive impairment. Antipsychotics are generally effective in treating positive symptoms, but the treatment of negative symptoms and cognitive impairment remains a clinical challenge and a major unmet need in the treatment of schizophrenia. Negative symptoms have a substantial impact on the day-to-day functioning of patients and constitute the main barrier to a better quality of life for patients with schizophrenia.

AIMS: To develop new atypical antipsychotic targeting dopamine D_2/D_3 receptors with D_3 selectivity to provide solution on the unmet medical need to treat predominant negative symptom of schizophrenia.

RESULTS: Cariprazine is a new orally active and potent dopamine D_3 and D_2 receptor partial agonist with preferential binding to D_3 receptors, which has demonstrated efficacy in treating various symptoms of schizophrenia in short and long term treatment trials. Cariprazine is approved in the US for the treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder in adults. In the post hoc analysis of short term efficacy trials, cariprazine demonstrated significantly greater improvement over placebo in a subset of patients with high levels of negative symptoms. In an adequately designed clinical trial in predominant negative symptom patients cariprazine showed superiority over risperidone both on the symptoms and the personal and social performance of patients. Clinical developments of cariprazine are ongoing for bipolar depression (BD) and major depressive disorder as adjunctive therapy (MDD).

CONCLUSIONS: Cariprazine with its partial agonist property and D_3 selectivity on dopamine receptors as well as with marked efficacy on predominant negative symptoms of schizophrenia is a unique representative of third generation antipsychotics.

O-56

Changes in pharmacokinetics in patients with chronic heart failure

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Chronic heart failure can lead to changed body composition and cachexia. Cachexia is a unique process of weight loss resulting from constant activation of inflammatory processes caused by underlying chronic disease like cancer, chronic heart failure, chronic obstructive pulmonary disease, etc. In patients with chronic heart failure, the disease itself and changes in body composition and cachexia may influence drug pharmacokinetics. Additionally, body composition may influence the estimation of renal function if it is based on serum creatinine concentration. Patients may lose their muscle mass despite unchanged total body weight and this may result in decreased serum creatinine concentration regardless of their renal function. On the other hand, renal function is one of the key clinical parameters to be monitored in heart failure patients. Besides predicting mortality, it can importantly change renal excretion of drugs. A significant proportion of patients with chronic heart failure develop a rapid decline in renal function, regardless of their baseline renal function. In pharmacotherapy of heart failure, inhibitors of angiotensin convertase enzyme and beta blockers are used to improve survival and reduce number of hospitalizations.

In patients with chronic heart failure we evaluated the pharmacokinetics of bisoprolol and ramipril, including longitudinal changes, and the influence of changed body composition and cachexia on drugs pharmacokinetics (1). Moreover, we assessed the performance of creatinine-based renal function estimating equations in monitoring changes of renal function in chronic heart failure patients, and the effect of body composition on the equations performance (2).

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O-57

Safety an efficacy of vitamin D supplementation among elderly people

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BACKGROUND: Vitamin D is essential to maintain the health status and the normal funtion in multiple organs in human. The potential role in prevention as well as correlation in certain morbidities, have been revealed recently. Advanced age, four-wall trapped lifestyle, low exposure to sunlight and insignificant

dietary Vit-D intake are the major factors associated with VitD deficiency.

AIMS: An observational study conducted between 2015 -2017 included elderly patients hospitalized in geriatrics facilities at Zala-megyei Szt Rafael County Hospital. Patient characteristics by key medical history parameters and diagnoses were analyzed by the severity of VitD deficiency. The efficacy of standard dose with a combination of loading –maintenece Vit D supplementation were assessed.

RESULTS: Significant Vitamin D deficiency was observed among the elderly people. The deficiency was over 90%, and half of the subjects who had no prior vitamin D supplementation did not reach the level of serious deficiency. The efficacy of Vit D treatment elevating the 25(OH)D levels were observed in most patients receiving at least 1000ÍU daily doses in average. Treatment with slow uploading doses – 30000 IU /week for 3 month significantly increased the median 25(OH)D levels. over one year period.

CONCLUSIONS: Vit D deficiency among hospitalised elderly people are significant and may have critical impact on their health status. Periodic support with Vitamin D may not provide enough sources to maintain the recommended 25(OH)D levels. A therapy starting with a slow loading dose of 30000 IU/week for 3 month proven to be efficient and to reach the targeted levels. A continuous maintanence doses are necessary even over the summer period.

This work was supported by EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" project.

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O-58

The efficacy of ginger (Zingiber officinale) for the prevention of postoperative nausea and vomiting

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BACKGROUND: Postoperative nausea and vomiting (PONV) is one of the most common and distressing outcomes occurring within 24 hours after surgery, affecting patients undergoing general anaesthesia. PONV may lead to several secondary complications, such as aspiration pneumonia, wound disruption, gastric herniation, dehydration and fatigue. Ginger has been used in the treatment of nausea and vomiting for thousands of years. Recently several randomized, placebo-controlled clinical trials have been conducted in order to evaluate the effects of ginger on PONV.

AIMS: The aim of our work was to assess the efficacy of orally administered ginger on PONV compared to placebo based on the available clinical data. Literature searches were conducted through EMBASE, PubMed and WOS databases. Human, placebo-controlled clinical studies of patients undergoing any types of surgery, receiving pharmacological doses of ginger *per os* were included. Only clinical studies with explicit description regarding the extract of ginger were analyzed..

RESULTS: Eleven randomized trials including a total of 1157 patients were pooled for statistical analysis. The investigated primary outcomes were 1) presence of postoperative nausea or vomiting, 2) request of rescue antiemetic drugs, and 3) changes in nausea and vomiting scores. Subgroup analyses were performed with different doses of ginger. To assess the efficacy of ginger on PONV a frequentist approach random effect analysis was performed, calculating 95% confidence interval for the pooled effect and two sided *P* value. Statistical heterogeneity was explored by Chi square test and I-squared statistics.

CONCLUSIONS: The results of our analysis demonstrate that ginger intake may reduce the risk of postoperative vomiting, and ameliorate nausea scores. However, only doses of ginger not less than 1000 mg were significantly better than placebo. The effects of ginger on postoperative nausea and rescue antiemetic request were not statistically significant.

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POSTERS

POSTER SECTION 1A
NOVEL DELIVERY SYSTEMS 1

P1A–1
Melt-electrospinning: a novel method for formulating and improving the solubility of poorly water-soluble drugs

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BACKGROUND: Solution or melt electrospinning (MES) are effective methods for fabricating nano- or micro-scale drug delivery systems (DDSs), or scaffolds for biomedical applications. Formulation of melt electrospun fibrous solid dispersions is a novel approach to improve the solubility of poorly water-soluble drugs1. The combination of several factors related to the process (amorphization, stabilization and void of any solvents) makes MES an attracking tool to be investigated to address poorly soluble drugs.

AIMS: The objective of this study was to prepare and characterize DDSs fabricated by MES using indomethacin (IND) as a model drug, and polyvinylpyrrolidone (PVP)/Soluplus (SOL)/xylitol (XYL) as carriers. Moreover, the effects of formulation on the dissolution behavior of IND was investigated.

RESULTS: Melt spun fibers (MSFs) were successfully prepared and analyzed using XRPD, FTIR, DSC and SEM. The dissolution studies were carrier out at pH 6.8. Solid-state characterization confirmed the presence of amorphous IND. The dissolution (drug release) from MSFs was superior compared to that obtained with pure crystalline IND alone, or with the corresponding physical mixtures (PMs).

CONCLUSIONS: The results demonstrate that MES can be used as an effective tool for fabricating micro-scale fibers (fibrous solid dispersions) for poorly-water soluble drugs. The dissolution rate of IND can be significantly improved compared to that of pure drug and PMs.

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P1A–2
Evaluation of techniques and possibilities for oral delivery of antidiabetic peptide drug – liraglutide – in a novel delivery system

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BACKGROUND: Liraglutide (NN2211) is a long acting Glucagon like peptide-1 (GLP-1) analog with 97% homology to human GLP -1. It is approved by FDA for the treatment of diabetes mellitus type 2 and for chronic weight management of adults delivered through subcutaneous injection1. Since this invasive route is associated with many problems leading to insufficient patient compliance, the oral route should be aimed, providing a patient friendly administration in addition to mimicking the physiological route of GLP-1 from intestine to circulation2. However researchers should overcome the major obstacles concerning the oral liraglutide delivery, including the low stability through GI tract and low intestinal permeability.

AIMS: The aim of this presentation is firstly to evaluate the up to date strategies for oral peptides delivery, especially GLP-1 and its analogs and secondly to share a development plan according to Quality by Design (QbD) methodology for the early development of these dosage forms, and thirdly to give a report on the preformulation studies prior designing a final dosage form.

RESULTS: The following solutions can be evaluated to be a good selection for enhancing the oral bioavailability of the peptide drug by either protecting the drug from the harsh environment through the GI tract or improving its intestinal permeability: polymeric nanoparticles and cell penetrating peptides. These solutions in a proper combination could lead to a promising result, according to the results of the literature review. Quality Target Product Profile is to be defined as well as Critical Material Attributes and Critical Process Parameters as a part of QbD methodology. As a part of the preformulation study PLGA, Eudragit RS PO and Eudragit RL

PO were selected as polymers for preparing nanocarriers; the suitability of the double emulsion evaporation method is under evaluation at present.

CONCLUSIONS: According to the evaluation of the available literature and industrial data, evidences were found, that the achievement of the oral delivery of liraglutide leads to an improved patient adherence. As there are many critical steps in formulation as well as a careful selection of additivies is also a challenge in case of this type of products; authors strongly emphasize the application of QbD methodology in the early development stage as well as doing careful preformulation studies prior to dosage form design.

The work was supported by Foundation for Development of Pharmacy Education at University of Szeged.

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P1A–3

Development of a floating gastroretentive dosage form by melt foaming

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Introduction: Gastroretentive drug delivery is advantageous in such cases when the active ingredient has narrow absorbtion window or gastric targeted release is aimed. Based on the retentive mechanism we can distinguish categories like low- or high density based, mucoadhesion-based , size dependent or magnetic anchored forms.[1]

Aims: We aimed to develop and create a drug delivery system based on its high-porosity and low-density by foam formation after melting the components. We were also interested to determine the key factors affecting the elementary properties of the carrier, such as floating ability, foam properties by electron microscopic imaging. We also tested the in vitro drug release and texture changes during dissolution. As a possible API we used metronidazole.

Results: At start we designed and built a lab scale agitator and a suitable vessel to melt and to dose the molten mixture into size 00 gelatine capsules. After selecting the possible excipients we revealed, that the presence of lipids and surfactans such as PEG 4000, stearic acid or Labrasol was essential for the foam formation beside heavy agitation. Our EM pictures confirmed that we successfully created a carrier with closed cell structure. The prepared foams showed a hard structure even on body temperature. PEG and Labrasol alone was not enough to prepare foams with desired floating ability. From the initial density of 1,22-1,29 g/ml we decreased it to 0,78-0,92 g/ml target values. The dissolution studies showed that the more stearic acid was added to the mixture the slower drug release was detected. The 90% of the API was released within 10 hours.

Conclusion: We can summarize that we developed a novel method to prepare solid and low density drug delivery system with zero floating lag-time. The prepared samples showed prolonged drug release and hard structure with the ability to remain in the stomach for several hours.

This work was supported by EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" project.

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P1A-4

Formulation and evaluation of innovative, chitosan based mucoadhesive buccal drug delivery films

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BACKGROUND: Nowadays, the buccal administration of mucoadhesive films is very promising. It provides convenient dosing and patient compliance is good, considering its small size and easy application.

AIMS: Our aim was to produce chitosan based films, which can provide a small amount of active substance absorption through the buccal mucous membrane, thereby avoiding the hepatic first pass effect. During the formulation, we used ascorbic acid (AscA) in different concentrations (2-5%). It provided acidic pH, and it has permeation enhancer properties as well. We compared the AscA effects on the properties of films with films prepared with acetic acid (AA). Each film contained glycerol as plasticizer in the same quantity.

RESULTS: We examined the identification crystalline form in the films with X-ray powder diffractometry (XRPD).Spectra were recorded with a BRUKER D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany). The FTIR spectra suitable for structure analysis as well. The tensile strength was tested with a device and software developed in our Institute, the in vitro adhesion force of the film on mucin solution as well. The mucoadhesion force was examined by calculating the films' surface free energies (SFE) based on results from contact angle measurement with OCA 20 (DataPhysics Instruments GmbH). Higher AscA concentration caused higher plasticity in the films against AA containing films. AscA also modifies the mucoadhesional force, compared to AA films it is decreased to different extents. The XRPD spectra show us that the highest AscA amount did not build into the structure of the films, same as the FTIR spectra. The surface free energy was higher when using AscA than with AA.

CONCLUSIONS: Using AscA is advantageous in case of surface free energy, and from the mucoadhesion aspect the 4% of AscA composition proved the best.

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P1A-5

Alternating current electrospinning, a novel method for preparing drug-loaded amorphous solid dispersions

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BACKGROUND: Preparing amorphous solid dispersions of the growing number of poorly water soluble drugs can overcome the hurdle of reaching high bioavailability in the field of oral dosage forms. Two-thirds of the marketed solid dispersion-based products apply cellulose ethers as carriers due to their ability to prevent the drug from precipitation during dissolution and maintaining the high energy amorphous form of the drug for a long time. Alternating current electrospinning (ACES), the high-yield version of the widely investigated direct current method (DCES) is a promising novel way to prepare amorphous solid dispersions, although despite its benefits, it has not come into great interest yet in the field of pharmaceutics (1.).

AIMS: ACES was explored to prepare improved drug-release amorphous solid dispersions of poorly water soluble drugs with high productivity while maintaining excellent fiber quality. Cellulose ethers of great importance in pharmaceutics were intended to use as polymer carriers, although their poor spinnability required the investigation and modification of solution properties to improve the electrospinning process.

RESULTS: Conductivity of the polymer solution was found to be of great importance during ACES. After optimizing the solution conductivity and adding high molecular weight polyethylene oxides as active fiber-forming agent, multiple times higher productivity was achieved with ACES compared to DCES while maintaining the same good quality fibers. DSC and XRPD measurements showed that the drug turned into amorphous in the electrospun samples. Dissolution tests showed remarkable increase in drug release rates.

CONCLUSIONS: The results demonstrate that alternating current electrospinning is a promising new technique to produce drug-loaded polymeric mats at high throughput rates than the conventional direct current method.

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P1A-6

Mesoporous silica nanoparticles within nanofibers – novel antibiofilm strategy

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BACKGROUND: Biofilms are microbial communities together with polymeric extracellular matrix which are known to be the main reason for the development of resistance to antimicrobial agents and persistent and chronic bacterial infections (1). Mesoporous silica nanoparticles (MSN) as drug-carriers are able to pass through the cell membranes as well as biofilm matrices and provide better treatment outcome (2). However, the effica-

cy of MSN in killing the bacteria within the biofilm can be increased by using novel delivery platforms for the therapy such as MSN loaded electrospun nanofiber matrices.

AIMS: To design and develop MSN loaded into electrospun nanofiber scaffolds as novel antimicrobial agent delivery systems used for the prevention and eradiction of mono/poly microbial biofilms.

RESULTS: Prepared MSN consisting FITC labelling for tracking and polyethyleneimine surface functionalization were prepared and characterized using fluorescent microscopy, SEM and dynamic light scattering. Spherical shaped MSN had a mean size of approximately 250 nm and net positive surface charge. Stable MSN dispersion was electrospun together with a hydrophobic carrier polymer obtaining fibers mostly having a diameter of 260 nm, but there were also some larger fibers observed (diameters up to 1500 nm). The presence and distribution of MSN within the electrospun fibers was nicely shown using elemental analysis of SEM. The selection of appropriate polymers as well as solvents is crucial for successful electrospinning and obtaining stable drug delivery systems. The antimicrobial agent incorporation into the MSN will allow understanding whether the burst release together with prolonged drug release from electrospun nanofiber scaffolds can be achieved important for successful antibiofilm activity.

CONCLUSION: Mesoporous silica nanoparticles (MSN) were successfully incorporated into nanofibers using monoaxial electrospinning. Further studies will investigate the incorporation of various antimicrobial agents and the antimicrobial efficacy of the developed platform during i*n vitro* biofilm studies using relevant bacterial strains.

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P1A-7

The effect of sodium stearate on the aerosol performance of meloxicam potassium using a carrier-free procedure

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BACKGROUND: The development of dry powder inhalation systems (DPIs) led to the new generation of formulations. Instead of a traditional lactose-base formulation, carrier-free alternatives can be applied to reach better aerosolization behaviour of the drugs. Our previous work focused on the DPI formulation of meloxicam potassium (MXP), which is a novel synthetized salt form of meloxicam. Different types of hydrophilic additives were used to improve its aerodynamic properties. The pulmonary application of MXP is a novelty for local anti-inflammatory treatment because it does not exhibit aspirin-like hypersensitivity reactivity.

AIMS: The aim of our present work was the formulation and investigation of the DPI form of MXP containing sodium stearate in different concentrations (0-2 w/w%). Spray dried formulations were characterized in terms of size distribution, morphology, density, cohesivity, *in vitro* drug release in lung media and *in vitro* lung deposition.

RESULTS: Because spray drying dos not overcome the hydroscopic and cohesive nature of the powder, the incorporation of a lipophilic agent could offer a solution to these problems. The produced particles exhibited 2-3 μm size, low density and spherical form. The fine particle fraction was more than 80 %, however, the fine particle dose converted to % was around 60 %. 2% of sodium stearate resulted in the best product.

CONCLUSIONS: This study has shown that lung deposition could be influenced by modified morphology and size of the drug and the application of an adjuvant. The structure of the micronized drug (crystalline/amorphous) could affect the bioavailability and stability of the produced DPI, too. The pulmonary application of MXP is a novelty for local anti-inflammatory treatment; at present, MXP-containing DPI products are not marketed for pulmonary therapy.

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P1A-8

Microencapsulation of probiotics as biotherapeutic agents for their local delivery

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BACKGROUND: The delivery of probiotics to the different sites of action within the human body can help to prevent or even treat several diseases. The action of priobiotics is either based on the shaping of local microbiota or interacting with host cells resulting in the reversal of disease progression (1).

AIMS: The primary aim was to develop a delivery system for the probiotic bacteria, which were isolated from healthy individuals and to deliver them localy. The goal was to encapsulate probiotics into chitosan-coated Ca-alginate microcapsules produced by the prilling of lamellar liquid jet by membnane vibration technology. This enable adequate delivery of the probiotic bacteria as well as to increase their stability during storage.

RESULTS: Using different alginate concentrations (0.75 – 1.6 %), various excipients: lactose (filler), glycerol and trehalose (cryo- and lyoprotectants), chitosan (polyelectrolyte coating), microcapsules of 120 - 150 μm in diameter were produced, which were then additionally stabilized by freeze-drying. Their zeta potential switched from negative (- 10 mV) for uncoated to positive (+ 10 mV) for chitosan coated microcapsules. Stereo and scaning electron microscopy allowed us to examine the influence of chitosan-coating on surface morphology modification. The probiotic encapsulation efficiency was high; up to 1×10^9 of colony forming units per gram of dry microcapsules. A delay of probiotic release for at least 3h was shown for the coated microcapsules. The viability and stability of incorporated probiotics in such freeze-dried microcapsules has been shown to last at least for one month.

CONCLUSIONS: Chitosan-coated Ca-alginate microcapsules were proved as a promising delivery system for probiotics, enabling their sustained relese and providing easier handling as well as increased stability of encapsulated bacteria compared to those thar were only freeze-dried.

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P1A-9

Development of a lipid based drug delivery system containing antibiotics for the treatment of periodontitis

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BACKGROUND: Periodontitis – caused by anaerob Gram-negative bacteria – is the chronic inflammatory disease of the gingiva, which without proper treatment may lead to tooth loss. Antibiotics have been widely used in the treatment of periodontitis and could help eliminate pathogens responsible for the disease.

AIMS: Our aim was to develop lipid based drug delivery systems containing antibiotics which can be administered subgingivally and can provide sustained release of antibiotic compounds for at least one week. Biodegradibility is a key property of the formulations because it is important to help the periodontal pockets disappear and to allow the tissue of the gingiva to return to its healthy state.

RESULTS: We investigated the effect of the ratio of different lipid bases and the effect of the various concentrations of the surface active agents on the consistency, the wettability of the systems, the swelling and degardation properties, and the drug release. A preliminary microbiological investigation was also carried out in order to measure antimicrobial effectiveness of formulations. On the basis of the results the optimal composition was determined. The proper ratio of the lipid components can provide a suitable structure and an appropriate consistency with sustained release of the antibiotic agents.

CONCLUSIONS: We successfully developed a lipid based biodegradable drug delivery system containing antimicrobials for the treatment of periodontitis. With the adequate concentrations of the components, sustained release of the active components is possible.

The work was supported by Foundation for Development of Pharmacy Education at University of Szeged.

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P1A-10

CharacterIsatIon and EVALUATION OF Targeted LIPOSOMES. I - In vItro studIes

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BACKGROUND: Liposome-derived carriers have advantages such as their diverse range of morphologies, compositions, abilities to envelope and protect many types of therapeutic biomacromolecules, lack of immunogenic response, and their differential release characteristics. Also, they can be used to deliver a molecular cargo such as DNA for therapeutic benefit[1,2]. This type of gene delivery systems for therapeutic applications remains limited by their poor ability to escape from the endosomal compartment and to translocate DNA into the nucleus. Peptide carriers that combine DNA binding and membrane destabilising properties have been demonstrated to promote gene transfer into cultured cells and living animals[2]. We have recently described a new peptide-based[3] gene delivery system, prepared by cationic polymer which was covalently linked to DOPE, and conjugated with peptide 18 and peptide 563 which are specific for breast and prostat cancer, respectively.

AIMS: In our study we designed and prepared cationic liposomes for cancer treatment plasmid. We prepared liposomes with most widely used method[4], named as lipid hydration method. Their particle size and and zeta potential measurements were performed using an aqueous dip cell in the automatic mode by Zetasizer Nano ZS. The morphology of the lipoplexes were visualized by transmission electron microscopy. Encapsulation efficiency and loading capacity of the formulations was calculated. In-vitro release and their cyctotoxity studies were also performed.

RESULTS: The polymer which is as widely studied as PEG and shares many of the desirable features of PEG was synthesized by cationic ring opening polymerization of 2-ethyl-2-oxazoline. The prepared polymer was covalently linked to DOPE, and conjugated with peptide.

CONCLUSIONS: Lipoplexes of DNA may cause positive zeta potential (24 to 39 mV), low cytotoxicity (cells remaining 86-98%), with a proper particle size (around 100nm), that might contribute to the high transfection efficiency and seemed to be more efficient carriers for in vitro gene transfer. Further studies were carried on to determine their stability and efficacy on animal model transfection process.

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P1A-11

Formulation and characterization of dermal films for wound healing

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Wound healing is the natural process of regenerating the dermal and epidermal tissue of the body. It is the process that brings back the damaged part of the body as normal as possible [1]. The dermal film technology has proven to be fastest, easiest, safest and most economical way to help wound to heal. Hydrogels are ideal biopolymeric pharmaceutical forms for the treatment of skin wounds [2].

The aim of this study is to prepare dermal patches and evaluate wound healing potential with various polymers to be used topically in wound infections.

Different concentrations of sodium alginate and chitosan were used to prepare films. Glycerin, propylene glycol or PEG 400 at the range of 1-20 % was used as plasticizers and films were developed by solvent casting evaporation. Films were evaluated with regard to percentage moisture loss, thickness, FTIR, weight variation, and pH. Also swelling studies were performed at different time intervals. Films were prepared successfully by solvent casting technique. Films had homogeneous appearances and could be easily removed from the petri dishes, except K9-K16 code formulation (sodium alginate %1, glycerin and PEG 400). The films had a thickness varying from 0.25+0.02 to 0.90+0.05 mm. The thickness of inserts increased when the plasticizer concentrations were increased. All prepared formulations indicated good physical stability. Moisture content of films was studied in order to determine the degree of hygro-

scopicity of the formulation. The moisture of the insert was found less than 1% at the end of 24 hours. During the swelling test the films swelled for 12 hours and the volume and weight of the films increased.

According to the obtained results, when the ratio of plasticizer was increased, the thickness, weight, moisture loss and swelling rate of the formulation were found to increase. Films developed with chitosan and propylene glycol may be offered as appropriate vehicles for wound healing.

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POSTER SECTION 1B – NANOPHARMACEUTICALS 1

P1B-1
Steroid-harboring nanoparticles provide anti-inflammatory response with less adverse effects

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BACKGROUND: Steroids are acknowledged anti-inflammatory drugs used in multiple conditions, including autoimmune disease. Steroids provide strong suppression of inflammation, however, their long-term utilization triggers numerous adverse effects including obesity, diabetes, osteoporosis, edema retention etc. As a result, only inflammatory flares are treated with steroid compounds, for short term.

AIMS: Our collaborative research team has produced nanoparticles of specific size harboring steroid compounds. In theory, due their specific size steroid-harboring nanoparticles trigger phagocytosis in monocytes and macrophages, but leave other (non-phagocytic) cells unaltered.

RESULTS: Our human *in vitro* data indicate that steroid particles show potent anti-inflammatory effect on monocytes / macrophages, equivalent to that of steroid solution. However, their adverse effects are reduced using non-phagocytic cells. Liver cells, for example, show increased viability with steroid particles as opposed to steroid solution.

CONCLUSIONS: Our working hypothesis was that steroid- particles of a specific size range can preferentially target monocytes / macrophages, the major mediators of inflammation. Other (non-phagocytic) cell types shall largely be unaltered by steroid particles, as opposed to steroid solution. This is confirmed by our data. Our technology allows for the production of regular steroid compounds with significantly reduced side effects, with the promise of long-term use in human.

P1B-2
Preparation and evaluation of loratadine nanosuspension by using precipitaion ultrasonication technology

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BACKGROUND: Nanoparticle engineering occupies the top of applied techniques as new,and effective breakthrough in drug design and delivery. Nanosuspensions are nanoscale drug dispersions stabilized by minimum amount of steric or/and electrostatic stabilizers. Nanocrystals could present enhancing saturation solubility and surface area, thus increased absorption and bioavailability (1). The classical bottom up method used is precipitation from antisolvent, where drug nanoparticles are formed by assembling of its molecules from organic solution. Loratadine (LOR) has been selected as API, it is a second generation H-antagonist frequently prescribed for treatment of allergic rhinitis, and other allergic conditions,it is characterized by poor water solubility, high permeation, and pH dependent solubility.

AIMS: This study is aimed for preparation of LOR nanosuspensions by precipitation to enhance LOR solubility, followed by characterization by measuring particle size, PDI, and zeta potential. A statistical analysis was applied to evaluate the effects of surfactant and stabilizer concentrations on these properties. Freeze dried nanoparticles were characterized by DSC,XRPD,SEM, and in vitro release patteren.

RESULTS: The mean particle size and PDI were in the range of 245-488nm and 0,08-0,24 respectively with negative zeta potential ranged from-3 to -27 showing their stability. DSC and XRPD indicated LOR crystallinity reduction.

CONCLUSIONS: Antisolvent precipitation with ultrasonication was a proper method to prepare LOR nanosuspensions with stable homogenous distribution. These nanoparticles can be used as intermediate products for furthur formulations.

The work was supported by Foundation for Development of Pharmacy Education at University of Szeged.

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P1B-3

Pickering emulsion of tea tree oil in water, stabilized with silica nanoparticles for onychomycosis topical treatment

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BACKGROUND: Onychomycosis is the most common nail infective disorder, which may be treated by topical and/or oral therapy. Because of the risk of oral therapy, which is the hepatotoxic side effect of antifungal drugs, topical therapy is usually recommended. The hard keratin and compact structure of nail plate act as a barrier to drug diffusion, and the hydrophilic nature of the nail plates also reduces the delivery of lipophilic and high molecular weight antifungal drugs (e.g. amorolfine, tioconazol) to the infection site. Owing to the aforementioned problems the topical treatment takes long time (10-12 months) and has a low cure rate(1). Some of the essential oils can be used as the alternative in Onychomycosis topic therapy, because of its antifungal activity, but their lipophilic character faces the same drug delivery challenge.

AIMS: Our aim is to prepare silica nanoparticle stabilized o/w type Pickering-emulsion (2) with antifungal active tea tree oil, investigate its diffusion in model membrane and nail plate and compare it to that of pure oil.

RESULTS: Hydrophilic silica nanoparticles were synthesised by Stöber method in one-step synthesis, which were characterized with DLS and TEM. The size range of the silica nanoparticles is 15 nm to 100 nm. We have performed a surface modification of silica nanoparticles with different amounts of ethyltriethoxysilane to tailor their hydrophilic/lipophilic surface character. The ratio of oil, water and silica nanoparticle was optimized to obtain emulsion with desired droplet size. The emulsions are characterized regarding their stability and droplet size. The variation of silica nanoparticle size, surface modification and emulsion composition resulted emulsions with droplet size from 100 nm to 800 nm.

CONCLUSIONS: At present we are working on the experiments, and the final results and conclusion will be shown at the conference.

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P1B-4

Influence of oil and cholesterol as wall components on the mean vesicle size of liposomes

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BACKGROUND: Nowadays liposome formulations offer excellent possibilities for the development of nano drug delivery systems (nanoDDSs). A great number of patents and articles deal with these formulations, and it is known that the mean vesicle size largely determines their applicability in therapy.

AIMS: Our aims were to investigate liposomes with different content of wall components and without active pharmaceutical ingredients. We were interested in how the mean vesicle size and distribution of liposomes can be influenced by the oil component and cholesterol content.

RESULTS: We produced the samples with different wheat germ oil (0-10 w/w %) [1] and cholesterol (0-10 w/w %) contents [2] using lipoid film hydration method on a laboratory scale. The investigations of the vesicle size of liposomes were performed with the dynamic light scattering process and laser diffraction particle sizing technique. 5 w/w % of oil content results in small vesicles, and the further increasing of oil content increases the vesicle size and polydispersity, too. Furthermore, experimental data shows that 7.5 w/w % cholesterol content resulted in the smallest vesicles. In the latter case d(0.5) is 147 nm, which is a good applicable particle size during a liposomal treatment.

CONCLUSIONS: Our experimental work is a preliminary investigation, which shows that the wall components of liposomes as oil and cholesterol can influence the vesicle sizes and size distribution, too. With a systematic design, it is possible to produce specified sized 'empty' liposomal form.

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P1B-5

Biocompatible low-energy nanoemulsions for curcumin dermal delivery – the effect of terpene oil and drug content

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BACKGROUND: Low-energy nanoemulsions (LE-NEs) are considered novel drug vehicles, able to meet the criteria of modern trends in designing drug carriers for highly demanding molecules. Curcumin (CU) – a polyphenol of natural origin, is a potent antioxidant, cancer chemopreventive and potential chemotherapeutic agent that appears opportune for the melanoma therapy. Due to its physicochemical characteristics, CU represents a challenging model drug.

AIMS: The objective was to inspect the critical formulation parameters and to develop a biocompatible LE-NE as delivery systems for CU, stabilized by polysorbate 80 and soybean lecithin, suitable for dermal application with potential to overcome the *stratum corneum* barrier. Knowing that terpenes are powerful chemical penetration enhancers, the goal was to investigate the influence of the eucalyptol (EU), as terpene oil, on performances of selected LE-NEs, by varying its concentration. Additionally, the effect of CU incorporation in the chosen formulations was aimed to be evaluated in terms of physicochemical and *in vitro* release properties, using vertical diffusion and immersion cells.

RESULTS: Developed formulations were hydrophilic, low viscous vehicles, with a mean droplet size (*Z-ave*) around 100 nm (depending on surfactant-to-oil ratio – SOR), narrow size distribution, desirable zeta potential and pH values, stable during short term monitoring. EU induced remarkable Z-*ave* reduction, but, contrastingly, CU incorporation increased this value. Different CU and EU contents had decisive influence on CU release from investigated samples.

CONCLUSIONS: Oil phase composition, SOR, as well as CU content proved to be the critical formulation parameters in LE-NE design. Next step should be evaluation of CU *in vitro*/*in vivo* penetration/permeation behaviour from developed LE-NEs, both with and without EU.

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P1B-6

Investigation of folate-targeted Ga-68-labeled nanoparticles as imaging agents for positron emission tomography

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BACKGROUND: Folate receptor (FRα) is one of the promising tumor associated targets for imaging of cancer, because these receptors are overexpressed on several cancer cell types, and their expression is limited in normal, healthy tissues. Nanoparticles from biodegradable and biocompatible biopolymers provide a robust nanoplatform with appropriate surface modification for both targeting molecules and even for PET radionuclides in a highly efficient and reliable manner. Biodegradable nanoparticles using tumor associate-receptor ligands (e.g. folate) for targeting have remarkable potential as diagnostic imaging agents in Positron Emission Tomography (PET) (1). This work focused on the development of folate targeted biopolymer based nanoparticles for preclinical PET/MRI imaging.

AIMS: The aim of this study was to evaluate the tumor targeting properties of the Ga-68-NODAGA-nanoparticle under *in vitro* and *in vivo* conditions using FRα positive KB (human cervix carcinoma) and FRα negative MDA-MB-231 (human breast cancer) cell lines.

RESULTS: In our *in vitro* Ga-68-NODAGA-nanoparticle uptake studies significant differences ($p \leq 0.05$) were found between the folate receptor

positive and negative cell lines after different incubation times. The ^{68}Ga-NODAGA-nanoparticles showed high specificity and binding affinity for folate receptor overexpressed KB tumor cells, nevertheless the cell survival was more than 98% based on MTT assay. These results showed strong correlation with our flow cytometric measurements where the number of FRα receptors were investigated. The *in vivo* biodistribution and the tumor uptake of Ga-68-NODAGA-nanoparticles were also studied in KB and MDA-MB-231 tumor-bearing SCID female mice using PET/MRI imaging. The *in vivo* PET/MRI studies indicated high tumor uptake with 6.31±0.25 T/M ratio and demonstrated that the ^{18}FDG positive tumor areas and the Ga-68-NODAGA-nanoparticle positive areas overlapped using folate receptor positive KB tumor xenograft.

CONCLUSIONS: In conclusion, the Ga-68-NODAGA-labeled nanoparticles are promising candidates for imaging folate receptor overexpressing tumor cells using positron emission tomography.

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P1B-7

Development and evaluation of micellar curcumin intended for the treatment of cutaneous T-cell lymphoma

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BACKGROUND: Curcumin is a natural molecule possessing variety of pharmacological effects but its poor solubility and stability limited its clinical use. Incorporation of curcumin into nanoparticulate delivery systems could overcome these drawbacks. This approach might enhance therapeutic potential of encapsulated curcumin for the treatment of cutaneous T-cell lymphoma as orphan disease.

AIMS: The aim of the study was to encapsulate curcumin in micellar nanoformulation and to evaluate its efficiency for the treatment of cutaneous T-cell lymphoma (CTCL).

RESULTS: Micellar formulation containing curcumin was developed using Pluronic as polymeric carrier. Incorporation of curcumin into micelles was performed applying different methods aiming to obtain optimal encapsulation efficiency. The resulted micelles possessed an average diameter less than 200 nm and negative surface charge. In vitro release tests showed an achievement of sustained release of curcumin. Cytotoxic studies in three CTCL cell lines (HuT 78, MJ and HH) revealed that micellar curcumin achieved lower IC_{50} values and is more suitable for combinations with other antineoplastic drugs than free curcumin. Fluorescence microscopy visualized that the micellar curcumin penetrated through the membranes of CTCL cells faster than free curcumin.

CONCLUSIONS: The encapsulation of curcumin in micellar formulation could provide better cytotoxic effect at lower dose, that might be considered advantageous taking in account the poor solubility and absorption of curcumin.

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P1B-8

Pickering foam formulation by wet nano-milling

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BACKGROUND: Pickering foams or emulsions are very interesting formulations because they are stabilized by solid particles instead of surfactants. We observed during formulation of a nano suspension of a hydrophobic API by wet ball milling spontaneous undesirable formation of a viscous foam, which was stabilized by solid nanoparticles dispersed in water.

AIMS: We have prepared a Pickering foam by the milling of a hydrophobic API suspension in a flow-through ball mill Netsch LabStar by zirconium dioxide balls as the milling media. We have characterized the particle size distribution (PSD) of the API particles in the foam by static light scat-

tering and Scanning Electron Microscopy (SEM). We have studied the 3D structure of the foam and calculated its porosity using micro CT and confocal optical microscopy.

RESULTS: A Pickering foam produced by the ball nano-milling process is stabilized by the solid particles of the hydrophobic API. The foam formation time is dependent on the initial surfactant concentrations used in the milling process. Mechanical properties such as viscosity are dependent on the milling time and increase because of increasing number of stabilizing particles and their surface area.

CONCLUSIONS: Solid nanoparticles can be used as emulsifiers for the stabilisation of the Pickering foams or emulsions, which have advantages compared to surfactant stabilized formulations. Sometimes the formation of a Pickering foam can be a spontaneous and unwanted phenomenon, which causes a change of mechanical properties of the material and makes the technological process more challenging. To avoid undesired complications of the technological process, it is important to know what causes the changes and to know how to avoid them. This was achieved by studying the undesirable Pickering foam produced by the formulation of a nanosuspension. The foam creation is significantly dependent on the surfactant concentration relative to the specific surface area of the hydrophobic API.

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P1B-9

Development of magnetically-responsive SPION-based drug delivery system

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BACKGROUND: The targeted drug delivery based on remote control over the distribution and accumulation of the nanocarrier in the body is very attractive in current pharmaceutical research and development, especially in the field of cancer treatment (1). Thus, nanostructures based on superparamagnetic iron oxide nanocrystals (SPIONs) represent a novel, very promising platform for development of novel delivery system, however, they still face some obstacles, which should be overcome to achieve optimal effectiveness. The main limitation of individual SPIONs is the too small magnetic force acting on them, when exposed to magnetic field gradient, thus resulting in their ineffective spatial guidance. This challenge can be overcome by assembly of multiple SPIONs into nanosized SPION clusters or magnetic nanochains (2). Magnetic nanostructures are usually coated with porous silica which offers unique properties for drug loading and, at the same time, it improves the compatibility of the nanosystem with biological environment. Therefore, such magnetically responsive nanosystems represent, due their multifuntional properties the great potential for the cancer treatment (3).

AIMS: The main aim of the present research was the preparation of (i) hollow magnetic SPION-based clusters and nanochains that form stable colloidal suspension and (ii) the development of a method for model anticancer drug loading and controlled release.

RESULTS: In the scope of the current study the hollow nanostructures based on well-defined SPION-based clusters of about 150 nm in diameter and magnetic nanochains with length of about 300-500 nm were successfully fabricated. To achieve colloidal stability of prepared nanosystems in physiological environment, their surface was additionally modified with hydrophilic polymers and the stability of the prepared system was evaluated in phosphate and HEPES buffer *in vitro*. The zeta potential measurements revealed the sufficient surface charge (between-25mV and -40mV) that is required for colloidal stability of nanodispersions. The initial results of drug loading experiments showed promising drug loading. The loading was performed by particle incubation in drug solution, however, the drug release experiments revealed very fast drug release from prepared nanodelivery system (total release ≤ 30 min).

CONCLUSIONS: The research revealed that hollow SPION-based nanostructures represent a promising nanomaterial for development of a magneto-responsive drug delivery system, however, the drug loading procedure should be further optimized in order to achieve better drug incorporation into the hollow particle nanostructures and controlled drug release.

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POSTER SECTION 1C PHARMACEUTICAL TECHNOLOGY 1

P1C-1

Parameter optimization of spherical agglomeration method

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BACKGROUND: In the industry area, direct compression is one of the most important techniques for the formulation of solid form drugs. For this the applicaqtion of this method, the active agent should possess appropriate parameters for example increased flow rate generated by large-size (>100 mm) and spherical crystals. For improving the morphology, spherical crystallization techniques can be used. These can be categorized into two groups: non-typical [1] and typical ones [2]. From our previous work it became clear that the non-typical methods, such as spherical agglomeration, are suitable for improving the morphology of ambroxol hydrochloride (AMB-HCl).

AIMS: This work aims at the optimization of the parameters of spherical agglomeration method. For this, a factorial design was applied and then the results were evaluated with STATISTICA for Windows program.

RESULTS: The potential critical parameters were as follows: agitation type and time, temperature differences between the solvent and the antisolvent, composition of the solvent system, saturation rate and feed rate. The average size, aspect ratio and roundness of the products were determined, then the ones with proper morphology were chosen for further experiments. Significant effects on morphology were revealed. The products were also examined by an individually-developed hardness test.

CONCLUSIONS: The application of horizontal shaker with shorter mixing times and lower temperature differences had a positive impact on the morphology of AMB-HCl. With the help of spherical agglomeration, the particle size increased up over an order of magnitude and roundness and aspect ratio improved, too. The hardness of the products was large enough to keep the spherical particles stable.

The work was supported by Foundation for Development of Pharmacy Education at University of Szeged.

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P1C-2

Aggressive conditions during primary drying as a new approach to optimize freeze-drying cycle of biopharmaceuticals

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BACKGROUND: Freeze-drying is the method of choice to dry formulations with biopharmaceutical drugs, typically unstable in aqueous media. This is usually done below glass transition temperature of maximally freeze-concentrated solution (Tg') to maintain physical stability, avoid the aggregation and preserve the activity of the protein, resulting in a lengthy and energy consuming process. However, it was recently shown that drying above Tg' or even above collapse temperature (Tc) is not necessarily detrimental for the stability of biopharmaceuticals, providing an attractive option for freeze-drying cycle optimization [1, 2].

AIMS: The aim of the present study was to reduce the primary drying time of a model monoclonal antibody IgG formulations (20 mg/ml) using aggressive conditions which were achieved by varying the shelf temperature and the chamber pressure, both directly impacting the product temperature (Tp).

RESULTS: In conventional freeze-drying cycle the Tp was -30 °C which is close to Tg'. With the implementation of the aggressive primary drying we managed to increase Tp to -24 °C which is above Tg' and Tc. Consequently the time of the freeze-drying process was reduced by up to 40 % (from 48 to 30 h) as opposed to conventional freeze-drying cycle. Although the Tp was in some

cases above Tc, macrocollapse was not observed. Additionally, other product quality attributes, such as reconstitution time and residual water content were also acceptable.

CONCLUSIONS: Aggressive conditions during primary drying present a prospective tool in shortening the freeze-drying time whilst ensuring quality attributes of the biopharmaceutical formulations.

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P1C-3

Unique laser coding technology to fight falsified medicines

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BACKGROUND: Counterfeit drugs pose a threat for health and they cause social and economic damage. According to WHO statistics, fake medicines represent 10% of the global drug trade and 50 % of medicines purchased over the Internet could be fake [1].

AIMS: According to Directive 2011/62/EU as regards the prevention of falsified medicines from entering into the legal supply chain, a unique identification should be put on each box of drugs [2]. Our team is working on the development of a technology to mark an individual traceability code directly on the surface of the tablet. Anyone with a camera-enabled phone and a suitable application installed should be able to authenticate these drugs.

RESULTS: We coated tablets with HPMC and PMMA polymers. To mark the coated tablet, we used different types of lasers: high energy ArF excimer pulse laser, semiconductor laser and Nd: Yag laser. After marking polymer films, we made an analytical quality control of them to check if there occurred any change during the laser intervention. The Raman spectroscopy showed a structure crack in a film treated with the semiconductor laser, while the excimer laser did not cause any significant change. Thermogravimetry showed that the decomposition of the material occurred sooner in films marked by semiconductor laser, in higher temperature ranges, which is probably due to the decomposition process that had already started during the laser marking process. We did not experience anything like this in case of using excimer laser. The pre- and post-laser structure was examined by SEM as well.

CONCLUSIONS: Results in this study showed that excimer laser could be the right instrument for marking the tablets with a unique code, which can be authenticated even by the patients themselves using a mobile phone.

The work was supported by Foundation for Development of Pharmacy Education at University of Szeged.

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P1C-4

The investigation of the connectability of continuous flow reactors and electrospinning

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BACKGROUND: Despite the various examples from other industrial sectors pharmaceutical technology still relies on traditional batch methods instead of continuous processes, albeit the investment and operating costs of the latter are lower and constant product quality is obtainable.

There have been many synthetic studies of drugs using continuous flow reactors, however, the direct formulation of the drug after the synthesis was found to be rather challenging. The only exemplary research on such an integrated system was conducted in the laboratory of the MIT [1]. Nevertheless, the way the interconnection was carried out was unfavorable for thermosensitive drug compounds.

Electrospinning provides a unique opportunity to convert the final liquid flow of the synthesis into solid product immediately. During the process micro- and nanofibers are formed in a gentle

way under ordinary circumstances by applying high voltage.

AIMS: The aim of this study was the development of a lab-scale production equipment in order to demonstrate the connectability of continuous flow reactors to electrospinning. The synthesis of acetylsalicylic acid was chosen as model reaction.

RESULTS: After the optimization of the reaction, we investigated the processability of the reaction mixture by electrospinning. As a result, highly water-soluble polymer fibers could be obtained. The purity, physical structure and state of the fibrous product was examined by different analytical techniques.

CONCLUSIONS: Electrospinning was found to be connectable with continuous flow reactors, and could be applied not exclusively for formulation, but to purify the reaction mixture as well.

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P1C-5

Hot-melt technologies to develop modified or targeted release hard capsules

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BACKGROUND: The convenience for patients and professionals to administer oral sustained-release capsules and tablets are well-known. [1] The enhancement of bioavailabilty and sustain drug release formulations can be achieved by using molten dispersions. PEGs, semisynthetic glycerides and their conjugates are favoured to be used as thermoplastic or meltable materials.

AIMS: In effort to develop modified release hard capsules, novel approaches were developed comprising pulverised lipids, e.g. Gelucires, stearic acid, cetostearyl alcohol, ethylcellulose as a suspending agent. Our research was conducted to prolong drug release, furthermore to simplify solid dispersion filling into diffent size hard gelatin capsules.

RESULTS: Following the pulverization of the lipids a powder blend was made with suspending agent and APIs, such as diclofenace-sodium or acetaminophen or metronidazole. Rational design of the compositions consisting of Gelucire 50/13, cetostearyl alcohol and ethylcellulose made it possible to fill certain blends into hard capsules, then create a monolithic matrix by heating the closed shells. Drying and its unfavourable effects, such as brittleness of the gelatin can be prevented if capsules are sealed in fullfilled conatiners which traps steam. The monolithic matrix succesfully sustained drug release over 8 hours in SIF. Texture analysis revealed that the formed block inside the shells are resistant enough to be packed or blistered. In an other series of experiments using metronidazole, a floating system was created with zero lag-time and prolonged drug dissolution. Floating force measurements and texture analysis were performed to assess the characteristics of the floating formulation.

CONCLUSIONS: Melt techniques are promising ways to formulated hard capsules with APIs showing different water solubilities and bioavailabilities. Our experiments confirmed that no granulation, pelletization or melt-filling is required to produce sustain-release capsules. Drug dissolution can be tailored by wisely chosen auxillary materials to alter hydration of dosage form. In case of the floating formulation in vivo imaging is planned to confirm gastric retention.

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P1C-6

Self- microemulsifying pellets prepared by fluid bed coating technology

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BACKGROUND: The results of modern approaches in the medicinal chemistry yield in the increasing number of poorly water soluble active pharmaceutical ingredients (API). Due to the enhanced dosing, transport, storage and patient compliance, the peroral application, especially of solid dosage forms, represents the most favourable root of administration, where the water solubility and the drug bioavailability play an important role in achieving an adequate plasma concentration and therapeutic effect. The various methods for enhancing water solubility, permeability and bioavailability can be employed, where the increasing focus is put to the solid lipid nano and/or micro particles and lipid based drug delivery systems (1).

AIMS: The object of the study was to convert liquid self-(micro)emulsifying system (S(M)ES), containing carvedilol as a model BCS class II API, into a solid formulation by a Wurster fluid bed coating technology.

RESULTS: The microcrystal cellulose pellets cores (Cellets 200) were subjected to the fluid bed coating process in a chamber equipped with a novel swirl air flow generator (2). The coating dispersion was composed of liquid SMES and matrix materials (e.g. lactose), enabling the incorporation of liquid SMES into the coating layer. HPMC and PEG 6000 solutions were additionally used to prevent the adherence of the pellets after each individual coating stage. In order to obtain a sufficient layer of deposited material through three consecutive coating stages, various process and formulation parameters were tested. The coated pellets were subjected to the image analysis process where the average diameter and circularity were determined. Additionally the amorphous form of the API in the coating layer of the pellets was confirmed by the differential scanning calorimetry. The pellet layer was dissolved in water and subjected to the photon correlation spectroscopy, indicating the spontaneous formation of (micro) emulsion. The dissolution profiles of the coated pellets indicate improved dissolution rate of the model drug in comparison to the crystalline form.

CONCLUSIONS: It can be conclude that the fluid bed pellet coating represents a promising technique for the SMES solidification and the groundwork for further investigations and development.

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P1C-7

Formulation of topical pharmaceutical foam to enhance cutaneous drug delivery

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BACKGROUND: Skin, particularly the uppermost layer-the stratum corneum-presents a formidable, largely impassable barrier to the entry of most compounds. There are two major challenges in topical drug delivery. Besides the drug solubilization and adequate penetration of the stratum corneum, the patient adherence to treatment is also important due to the particularly low compliance in topical drug administration. Pharmaceutical excipients are able to help address these challenges. These compounds are able to deliver effective drug solubilization and modulation of drug penetration through the stratum corneum. These excipients can be very safe and highly tolerable. Moreover the applied components are enabling the formulation of diverse topical bases with excellent texture and sensorial properties which improve patient experience and promote adherence.

AIMS: The objective of this study was to formulate safe dosage forms with enhanced cutaneous drug delivery.

RESULTS: Physical properties of the formulations have been evaluated by various measurements. A series of in vitro biocompatibility tests had been performed to ensure safety in application. To complete our examination; HaCaT permeability assays have been deployed as well. These studies have demonstrated that the formulated foam compositions have the ability to deliver the API at an increased rate compared with other vehicles.

CONCLUSIONS: These results suggest that the these foams utilizes a nontraditional "rapid-permeation" pathway for the delivery of drugs. It is likely that components within the foam act as penetration enhancers, and reversibly alter the barrier properties of the outer stratum corneum, thus driving the delivered drug across the skin membrane via the intracellular route. This is in contrast to traditional topical delivery vehicles, which must first rely on hydration of the intercellular spaces in the stratum corneum to achieve drug delivery

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P1C-8

Formulation and investigation of baicalin in Self Emulsifying Drug Delivery Systems

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BACKGROUND: Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and the lipophilic compound, which are spontaneously form oil-in-water (o/w) emulsions upon mild agitation followed by dilution in gastro-intestinal fluids[1]. Baicalin is a flavone glycoside, extracted from the roots of Scutellaria baicalensis Georgi. It was shown, that the poorly water soluble and poorly permeable polyphenolic flavonoid has remarkable pharmacological effects including antioxidant, antimicrobial and anti-tumor actions. Baicalin is classified as class IV. according to the Biopharmaceutical Classification System (BCS)[2].

AIMS: The aim of the study was to investigate the thermodynamic solubility of baicalin in different types of surfactants and oils. Optimising the ideal oil/surfactant/co-surfactant ratios to achive minimal droplet sizes and stabile nanoemulsions. Adding the best precontentrate to a solid carrier, and after drying preparation of pellets by extrusion-spheronization method. After reconstitution of the pellets determine the droplet sizes and dissolution profiles in different pH dissolution medias.

RESULTS: Physical characterisations of matrix pellets were performed and all of the investigated parameters have met the Ph. Eur. 9. requirements. Reconstitution from the solid carrier was succesfull in all three different dissolution medias, nanoemulsion formulation of baicalin significantly improved its dissolution rate.

CONCLUSIONS: The low aqueous solubility of baicalin can be improved by SEDDS, and the preconcentrate could be effectively adsorbed to a solid carrier.

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P1C-9

Robust compression of multilayer enteric coated pellets enabled by dry powder layering

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BACKGROUND: Robust technology and particle formulation is needed in order to compress functionally coated pellets into multiple unit tablets. Main challenges that have to be solved by design of formulation and technological process are minimization of polymer film damage and assurance of tablet dose uniformity. Polymer film damage stems from inter-pellet contacts and contacts of pellets with walls of tableting die and punches during compression. Drug dose variability is primarily caused by segregation of pellets within tableting mixture.

AIMS: The aim was to develop multilayer delayed release pellet formulation and associated technological processes that would be applicable to pellet tableting process.

RESULTS: The concept of forming cushioning layer around film coated pellets was employed [1]. However, compressibility of microcrystalline cellulose as a cushioning agent was retained by dry powder layering process rather than via layering with organic suspension. Dissolution testing of 11 mm biconvex tablets, comprised of enteric coated pellets with cushioning layer and extragranular phase, demonstrated less than 5 % of model compound release after 2 h in acidic conditions or even less, if mutilayer pellets contained additional intermediate layers of HPMC and polyethylene glycol. Polyethylene glycol film, that acts as a lubricant and reduces shear between cushioning layer and enteric film, enabled compression of sole powder layered pellets into tablets with improved hardness, reduced friability and little change in delayed release behaviour.

CONCLUSIONS: Powder layering approach and inclusion of intermediate lubricant layer proved to be successful strategies in designing multilayer delayed release pellets applicable to tableting process.

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P1C-10

Taste masking of enalapril maleate by various techniques

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BACKGROUND: Providing of a pleasant taste is of crucial importance for oral formulation especially those, intended for pediatric use. However, taste masking is a serious technological challenge. Enalapril maleate is bitter-tasting and could therefore be used as a model drug for this aim. In the present study we compare two approaches for taste-masking – spray drying and precipitation method, which results in a drug-polymer complex (DPC).

AIMS: The purpose of this study was to optimize the technological parameters for the development of DPC and spray dried microparticles of enalapril maleate for masking the bitter taste of the active pharmaceutical ingredient (API).

RESULTS: Taste masking requires the use of polymer that is insoluble in the saliva pH = 6.8 but dissolves in the acidic pH=1.2-3.0 of the gastric juice. This polymer should also not affect drug release profile. Eudragit EPO features the mentioned characteristics and respectively was chosen as a carrier. Aqueous dispersion of enalapril and Eudragit EPO was spray dried in order to obtain fine particles. The experiment was carried out under the following conditions: inlet air temperature 70 oC, aspiration 50-55%, peristaltic pump 20-25%. DPC was prepared by precipitation method. Solution of enalapril and Eudragit EPO in absolute ethanol was injected into 0.1 N sodium hydroxide under constant stirring at 600 rpm. The obtained powders were further characterized in terms of size, shape, production yield, moisture content and drug release. Both models showed satisfactory yield; DPC had irregular shape while spray dried particles were spherical. Dissolution test did not reveal any drug release within 5 min which proved the accomplishment of taste masking.

CONCLUSION: Spray drying and precipitation method using Eudragit EPO are reliable techniques for taste masking of enalapril maleate.

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P1C-11

Development of etoposide loaded poly(methyl methacrylate) and poly(hydroxyethyl methacrylate) tubular nanostructures

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BACKGROUND: Template-assisted synthesis, which provides a better of control of size and shape of materials, has become one of the most promising ways of fabrication polymer tubular nanostructures (1). Anodized aluminum oxide (AAO) membrane that contains highly ordered cylindrical nanopores with high aspect ratios, is one of the most popular templates for nanorod/nanotube fabrication by template wetting method

AIMS: In this study Etoposite loaded poly(methyl methacrylate) (PMMA) and poly(hydroxyethyl methacrylate) (P(HEMA) tubular nanostructures were prepared by template wetting of porous AAO membranes and characterised for structural analysis and drug loading.

RESULTS: Examination of SEM images showed that PMMA/P(HEMA) nanostructures were obtained successfully in nano dimensions in diameter and with smooth surfaced tubular form. EDX analysis did not show any traces of template (AAO)material like aluminum (Al) verifying effective removal of the template during the fabrication process. Drug entrapment efficiency and drug loading were found as 25.1% and 4.1%, respectively.

CONCLUSIONS: ETP was successfully loaded in polymeric tubular matrix. When the membrane was etched by mild aqueous acid, ETP loaded PMMA/P(HEMA) tubular nanostructures were liberated as drug carriers.

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P1C-12

Solidification of the self-microemulsifying system by a fluid bed granulation technique

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BACKGROUND: Over the last decade self-(micro) emulsifying systems (S(M)ES) are extensively investigated as one of promising technological approaches for improving bioavailability of poorly water soluble and permeable drugs (1). In addition, the effective methods for transformation of liquid S(M)ES into a solid formulations that merge the advantages of both systems are studied intensively (2).

AIMS: The aim of the present research was to convert liquid S(M)ES into self-microemulsifying granules by employing fluid bed technology that carries great potential for S(M)ES solidification scaling up.

RESULTS: Various solid carriers, binders and process related parameters (inlet air temperature and airflow rate, nozzle diameter and positon, atomizing air pressure and spraying rate) were tested. The Neusilin® US2, as the most appropriate solid carrier, enabled the manufacturing of granulate with a high drug loading at a high process yield. PVPs and HPMC of various molecular weights were used as binders, where PVP K30 as low molecular weight binder additionally inhibited the precipitation of BCS class II drug. The flow property of the manufactured granulates were proven to be in a correlation with the S(M)ES absorption capacity of the solid carrier, where the excess S(M)ES loading yielded in the poor particle flowability. The preservation of self-microemulsifying properties upon solidification process was confirmed by photon correlation spectroscopy, whereas prepared self-microemulsifying granules showed considerably increased drug dissolution profile as compared to crystalline form of BCS class II model drug.

CONCLUSIONS: Fluid bed technology equipment was shown as efficient and promising approach for transforming liquid S(M)ES into solid granulate, merging all the advantages of lipid based systems and solid formulations.

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P1C-13

The effect of different excipients in the soild dispersion-formulation of poorly soluble material using melt technology

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BACKGROUND: More than 40% of active agents are poorly water soluble drugs, therefore enhancement of solubility, dissolution rate and bioavailability of the drug is a very challenging task in drug development. Solid dispersion (SD) is a widely used method to form a stable amorphous product with improved physico-chemical properties, especially dissolution rate. SDs are the group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. A carrier/matrix should meet different criteria to be suitable for increasing the dissolution rate of a drug, such heat stable, chemically compatible, non-toxic, pharmacologically inert ect.

AIMS: During our work we introduced alternatives for the preparation of melted matrix containing active pharmaceutical ingredient by ternary and binary systems of PVP, PVA, Poloxamer, PEG, Mannitol and Soluplus.

RESULTS: By the preparation of Ishikawa diagram critical technological parameters were evaluated. Using XRPD and DSC the prepared samples were analysed compared with their physical mixtures. Amorphous and partial amorphous characters were detected. The hydrophilic excipients did not increase the dissolution rate of the API significantly as wetting agents through physical mixing. However the melted products presented more than 3-fold improvement, mainly in the presence of Soluplus or PEG.

CONCLUSION: The applied compositions and presented technological factors could offer a novel formulation methodology in the field of melt technology.

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P1C-14

Design of experiment of hydrophobic drug encapsulation using biopolymers : Particles size based study

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BACKGROUND: Microencapsulation is a process that creates a protection of the encapsulated molecules; it provides stability to these compounds and releases them in a controlled manner under specific conditions.

Complex coacervation is widely used for encapsulating lipophilic compounds like Sodium Diclofenac (SD) which is a potent non-steroidal anti-inflammatory drug with analgesic and antipyretic effects. However, due to its physicochemical action on the gastric mucous and inflammatory action on the small bowel and the colon, it counts for a risk factor of relatively high incidence of gastrointestinal side effects. Because of the mentioned side effects and its short biological half-life, SD is an ideal candidate for prolonged release preparations.

AIMS: The objective of this work is to study the influence and the interaction of different factors (stirring duration, drug concentration and carboxymethylcellulose (CMC) concentration) on the process of microencapsulation using an experimental design for the preparation of diclofenac microparticles by complex coacervation using gelatin and pectin as biopolymers.

RESULTS: The microscopic visualization of the different preparations reveals the existence of suspended particles as well as their irregular appearance, then the granulometric analysis shows a particles size variation between 25,54 μm and 57,35 μm. The statistical analysis reveals that the CMC concentration is the most important factor in this work; some of the interactions are also significative such as stirring duration-CMC concentration interaction. Finally, the responses surfaces study gave us the experimental domain which allows the elaboration of the smallest particles.

CONCLUSIONS: The results obtained demonstrate the effectiveness encapsulation of SD by complex coacervation in a pectin / gelatin polymer system.

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POSTER SECTION 1D PHARMACEUTICAL TECHNOLOGY 2

P1D-1

Solid-state characterization of albendazole-complex binary systems with pharmaceutical excipients

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BACKGROUND: Albendazole is an active drug against helminth and Giardia lamblia infections. The drug has a poor oral bioavailability; one of the attempts made to overcome this drawback was the obtaining of binary systems with cyclodextrins. Pharmaceutical excipients influence the pharmacokinetic properties of a pharmakon. The evaluation of the interaction between the drug and pharmaceutical excipients is a very important aspect of the drug stability within the pharmaceutical dosage form.

AIMS: The present study focuses on the evaluation of compatibility/incompatibility between the components of binary mixtures containing albendazole-cyclodextrin complexes and six pharmaceutical excipients. The binary mixtures were comparatively analyzed using thermal and spectral methods.

RESULTS:The search for potential interactions were carried out in the spectral regions of reactive functional groups of albendazole, where shifting of peaks, dissapearance of some bands and appearance of new bands designated interactions between the drug and the excipient. Powder X-ray diffraction patterns of albendazole complex were searched in the patterns recorded for binary mixtures. The infrared spectral data and the X-ray diffraction patterns indicated some minor interactions between complex and some pharmaceutical excipients, whereas in most of the cases, no interaction under ambient conditions were observed. Thermal analyses were used to confirm the results obtained by spectroscopic methods.

CONCLUSIONS: In this study we investigated the compatibility of albendazole complex with six pharmaceutical excipients using spectral and thermoanalytical methods. The results indicated a good compatibility between complex and the majority of excipients under ambient conditions and

under the induced thermal stress.

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P1D-2

Comparison of the physicochemical and mechanical characteristics of alginate and chitosan based films as wound dressings

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BACKGROUND: Chronic wounds are a great challenge for the medical care system with a growing number of people being affected [1]. New strategies in wound care need to be considered to overcome this problem. Natural polymers have shown to have desirable characteristics for usage in wound dressings which accelerate the wound healing process [2].

AIMS: The aim of the present study was to investigate and compare the relevant physicochemical and mechanical characteristics of alginate and chitosan based films intended to be used as wound dressings.

RESULTS: Alginate and chitosan films with gelatin in different compositions were produced by a casting/solvent evaporation method. These conventional films were compared with the corresponding films produced by 3D printing technology. Physicochemical characterization of material blends and the final films showed good miscibility and suitable properties for wound healing applications.

CONCLUSIONS: Natural polymers are suitable carriers for wound healing platforms due to their particular characteristics, such as biocompatibility, biodegradability and nontoxicity. These materials also support a wound healing process and/or have intrinsic antimicrobial activity. Combining these polymers with additional antimicrobial active substances and/or growth factors in the wound-care films provides an exciting opportunity for the local wound treatment.

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P1D-3

Mucoadhesion and rheological properties of poly(acrylates) gels for different mucosal drug delivery

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BACKGROUND: Drug administration via mucosal routes is frequently used for enhancing the local efficacy or bioavailability of systemic drugs. Poly(acrylates) are widely used for the preparation of mucosal formulations due to their good physical, chemical, and biological properties. Carbopol 974P and polycarbophil (Noveon AA-1) gels are found to be mucoadhesive and that they can rest on mucosal tissues for a long time (1,2).

AIMS: The aim of this study is to determine mucoadhesive and rheological and properties of poly(acrylates) gels for diffrent mucosal tissues. The storage and loss modulus were used as measurements for the rheological behavior. In addition, texture profile analysis and back extrusion tests were performed using different features of the Texture Analyzer. Mucoadhesion measurements were performed using a Texture Analyzer to determine the maximal detachment force of the gels from the mucosa and their work of adhesion. Bovine mucosa was used for the model mucosa; specifically, cheek, nasal, vagina, uterus, rectum, stomach, esophagus, small intestine and colon mucosa.

RESULTS: The storage and loss modulus of Carbopol 974P and polycarbophil gels are slightly reduced at low frequencies. It can be said that the Carbopol 974P gel has the best elastic character because it has the highest storage and loss modulus value. According to the results of textural profile analysis Carbopol 974P gel had an appropriate hardness and compressibility for application to mucosa, the highest elasticity showing good spreadability, and the highest cohesion to prevent the disintegration of the gel in the mucosa. The firmness, consistency, cohesiveness and index of viscosity were used to describe the texture characteristics of gels. Carbopol 974P gel showed the best mucoadhesive properties to the uterus but low adhesion to the buccal mucosa and esohagus. While polycarbophil gel shows the best mucoadhesive property to vaginal mucosa, this property is very low in buccal mucosa.

CONCLUSIONS: It was concluded that the rheological and mechanical properties of Carbopol 974P and polycarbophil gels are suitable for mucosal drug delivery. Carbopol 974P gels shows good mucoadesive properties in uterus and policarbophil is the best choice for the vaginal applications.

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P1D-4

Phenomenon of self-organized criticality in granule flowability examinations

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BACKGROUND: Self-organized criticality is a phenomenon and an important property of dynamical systems, which have a critical state. In the pharmaceutics flow properties of powders and granules can be described by this theory. These systems have a specific augmentation and reaching a critical point, avalanche behaviour of particles can be noticed.

AIMS: Our aim was to examine flow properties of medicated granules with classic methods which are supplemented by visual analysis technique to find significant contexts between flow properties and parameters of self-organized criticality phenomenon. This examination can serve additional information improving the process and development of multiparticular drug formulations. Our experiments were carried out using an experimental design including 22 samples. Variables of the design were: the type of the active agent applying a hydrophilic (paracetamol) and hydrophobic one (prednisolone), granulation method (using high-shear and oscillating methods), average particle size and the amount of the glidant (talc) added to the granules. Examinations included self-organized criticality based flowability, porosity, compressibility and surface properties of particles.

RESULTS: Our results were still under evaluation until the deadline of the transmission of the abstracts and will be presented on the conference.

CONCLUSIONS: Our conclusions were still under construction until the deadline of the transmission of the abstracts and will be presented on the conference.

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P1D-5

Evaluation of morphology of diuretic-incorporated polymeric microspheres

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BACKGROUND: Microspheres are drug form with size between 1-500 μm, in which the active substance is incorporated into the polymer matrix. They are multicompartment forms that allow to modify the release of the active substance.

AIMS: The aim of the study was to develop a technology for the preparation of microspheres containing the diuretic/furosemide incorporated into the Eudragit L30 D-55 matrix as well as the evaluation of their morphology.

RESULTS: Microspheres were prepared by spray drying technique using a Büchi Mini Spray Dryer B-191 (Büchi Labortechnik AG, Flawil, Switzerland). A standard nozzle with a diameter of 0.7 mm, pressure 3.5 bar and an air flow rate 600 l/h were used. The optimal spray-drying parameters of furosemide with Eudragit L 30 D-55 were as follows: aspirator capacity of 80%, T_{in}: 140°C, pump capacity of 10% and were selected based on morphology of the obtained microspheres, process efficacy and particle size. Morphological characteristics of microspheres were examined using scanning electron microscopy (SEM) analysis using Hitachi UHR FE-SEM SU 8010 ultra-high resolution microscope (Tokyo, Japan). The distribution of microsphere sizes was analysed using the Mastersizer 3000 laser diffraction particle size analyser (Malvern Instruments, UK) equipped with a dispersion unit. The particle size distribution was determined on the basis of the Fraunhofer model according to USP <429>. The analysed material of Furosemide-Eudragit

L30 D-55 in the 1:1 ratio contained the greatest amount (approx. 8%) of particles with 6.96 μm size. 90% of the particles were smaller than 21.4 μm. Weighted residual for 1:1 ratio was <1%, which indicates a good fit of the calculated data to the measured data.

CONCLUSIONS: The obtained results may allow to develop a new technological solution that optimizes furosemide therapy. The enteric form of this diuretic may also limit its side effects.

P1D-6

Differential scanning calorimetry and photon correlation spectroscopy as complementary tools for characterization of microemulsion hydrogels

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BACKGROUND: Microemulsion hydrogels (MHs) show great potential as (trans)dermal drug delivery carriers combining semisolid consistency of the hydrogels and percutaneous penetration/permeation enhancement of the microemulsions (1, 2). They consist of the biocompatible excipients including the components of the oil and water phase, the surfactants, the co-surfactants, and the suitable hydrophilic polymers. The complex structure of such drug delivery systems is poorly investigated.

AIMS: The purpose of the current study was to assess the influence of the different hydrophilic polymers on structure and drug solubilizing capacity of the MHs by using differential scanning calorimetry (DSC) and photon correlation spectroscopy (PCS).

RESULTS: The samples prepared with poloxamer 407 16% or xanthan 0.25% were homogeneous, clear to slightly opalescent viscous liquids, while a soft semisolid was obtained with chitosan 0.5%. For all samples the DSC analysis showed that the model drug ibuprofen was completely dissolved in a therapeutic concentration of 5%. Furthermore, the obtained endotherm patterns of the samples indicated that type and concentration of the polymer affected significantly the free and bound water ratio in comparison with the polymer-free ibuprofen-loaded microemulsion. Finaly, the results of the PCS analysis of the suitably diluted MHs demonstrated the nanodispersion structure likely comprising the oil droplets (<100 nm) dispersed in the aqueous phase. The different influence of the polymers on the droplet average size and distributions coresponded well with the DSC results.

CONCLUSIONS: The complementarity between the DSC and PCS results during the characterization of the structure of the different MHs was observed. Three structure models for the investigated MHs comprising different hydrophilic polymers were assumed.

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P1D-7

HPMC capsules as emerging solidification approach for self-microemulsifying drug delivery systems (SMEDDS)

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BACKGROUND: Development of the semisolid SMEDDSs is recently reported as a novel formulation approach for improving oral drug absorption (1). Filling of the semisolid SMEDDSs in hard capsules is scalable solidification strategy, however, major considerations are related with physical stability of the formulated solid dosage form (2).

AIMS: The semisolid SMEDDS filled in hard hydroxypropylmethyl cellulose (HPMC) capsules for oral delivery of the model drug acyclovir (ACV) was formulated by using the oil (medium chain length triglycerides), the surfactant (macrogolglycerol hydroxystearate), the co-surfactant (polyglyceryl-3-dioleate), the cosolvent (glycerol) and the viscosity modifier (macrogol 8000). The stability of the capsules filled with the semisolid SMEDDS was assessed during 3 months storage at 20±5 °C and at 5±3 °C (RH~60%) by performing: organoleptic and light microscopy evaluation, determination of ACV content by HPLC, and *in vitro* drug release study (after 0, 1, 2 and 3 months) using a rotating paddle method in phosphate buffer pH 7.2, at 37±1°C for 60 min.

RESULTS: Weight, colour and physical integrity of capsule shells were not changed during the evaluation period, and there was no significant change in drug particle size and content, at both temperatures. The drug release kinethics and the corresponding profiles of the ACV-loaded semisolid SMEDDSs, stored at both temperatures during three months, were similar ($0<f_1<15$). During the first 10 minutes a lag phase was observed and over a period of 30 min the cumulative % release of drug was approximately above 70%. The entire amount of the ACV was released from the semisolid SMEDDS in 50 minutes.

CONCLUSIONS: The results showed satisfactory physical and chemical stability of the investigated semisolid SMEDDS filled in HPMC capsules for at least 3 months at 20±5 °C and at 5±3 °C (RH~60%).

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P1D-8

Quantitative approach used Raman mapping for distributional homogeneity of different drugs in tablets

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BACKGROUND: Raman mapping is a suitable technique to examine the homogeneity in solid samples. Therefore it is used in the pharmaceutical field increasingly. Two kinds of technique have been developed for evaluating homogeneity in recent years.

AIMS: These two types of macropixel analysis were compared critically on samples prepared five different manufacturing technologies.

RESULTS: Two kind of API, imipramine and spironolactone were applied in three conventional and two continuous processing technologies. The homogeneity of distributions of 10% API was determined through Raman maps applying macropixel analysis method. Non-overlapping macropixel analysis (Poole-index) and calculation of distributional homogeneity indices (DHIs) were compared as a measure of homogeneity. Non-overlapping macropixel approach proved to be more sensible than DHI evaluation. For enhancing efficacy of DHI we suggest a correction by weighting scores and considering relative standard deviations. This way the capability of DHI can be improved significantly.

CONCLUSIONS: Using the modified DHI values the very slight differences between the continuous methods (the homogeneity of which are much higher than that of conventional technologies) could be quantified. Moreover the calculation of Poole-indices becomes unneccessary, of which calculation is time-consuming and needs more capacity than DHI.

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P1D-9

Experimental study of the effect of the particles shape on the mixing performance in pharmaceutical V-blender

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BACKGROUND: the particles shape is a important parameter having a significative effect on the powder properties [1]. It is therefore interesting to study particles shape before any pharmaceutical formulation.

AIMS: The aim of this work is to study the influence of the particules shape on the mixing performance. For this, two kinds of particles was used with differents aspect ratio which represente the ratio of the maximum and minimum diameter of the particles [0.17 and 0.83] at two rotational speed levels [10 and 27 RPM], for three loading profiles; Top bottom (TB), Front back (FB), and Right left (RL] with 50 % of tracer, in laboratry scale V-blender. The experimental study was carried out using disgn of experiments with NemrodW software.

RESULTS: The mixing performance was evaluated according the relative standard deviation (RSD) curves. It was found that the mixing time is very affected by the aspect ratio for the three loading profiles. Increasing the aspect ratio increase the mixing time for Top bottom loading profile, and decrease it in case of Right left and front back loading profiles. Regarding the effect of the rotational speed, increasing rotational speed enhance the mixing homogeneity for Right left loading

profile, and it was not significant for the other loading profiles.

CONCLUSIONS: From the experimental study, it was found that, the homogeneity of a mixture depends strongly on the initial arrangement of particles in the mixer and thus the loading profile. And the particles shape affect significantly the mixing time.

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P1D-10

Characterisation of polymer excipients by size exclusion chromatography and light scattering based detection

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BACKGROUND: Size Exclusion Chromatography-Multi Angle Light Scattering (SEC-MALS) is one of the few absolute methods for characterizing the polymers in solution. In combination with concentration refractive index detector the method additionally allows determination of average molecular weight, polydispersity and molecular weight distribution. Polyvinylpyrrolidon (PVP) and hydroxypropyl methylcellulose (HPMC), excipients from extended release matrix tablets, have been analysed by using SEC-MALS.

AIMS: Characterisation of PVP and HPMC polymers in matrix tablets.

RESULTS: The SEC-MALS for PVP and HPMC characterization was set up, properly developed and validated too. Both polymers have been initially separated by selective dissolving. For determination of purity of separation and extraction efficiency a RP-HPLC method was developed and successfully applied.

CONCLUSIONS: PVP, either K25 or K30 as excipients in matrix tablets have been identified. For the exact determination of PVP type the method of separation has to be refined as the difference between their average molecular weight is small. Second polymer, HPMC, represents according to the weight average molecular weight and molecular weight distribution most probably HPMC K15M.

*Dedicated to the memory of Prof. Dr. Istvan Erös, Faculty of Pharmacy, University of Szeged, Professor, Researcher and Friend.

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P1D-11

Effect of surfactants on microencapsulation with coacervation-phase separation method

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BACKGROUND: Microencapsulation is an adaptable method for incorporating sparingly soluble active ingredients, oxidable substances, proteins from biotech origin or viable cells into a drug carrier. Microsphere and microcapsule differ in their structure, but both contain the active ingredient encapsulated by optional polymers, providing the beads with increased stability and depending on the polymer characteristics, modified release. In combination with phase separation method Büchi-390 apparatus is capable of laboratory scale microparticle formation within a wide range (nozzle diameter 80 um- 1000 um) using the vibration nozzle method (VNM), where the laminar jet of drug solution is broken into droplets by an axial vibrational force.

AIMS: As surfactants are capable of influencing the droplet formation, our study primarily aims the investigation of the effect of different surfactants (e.g. Polysorbate 20 and 80) on the formation of microparticles using VNM method. The experiments also concern to observe the impact of the different process parameters (e.g. vibration frequency, feed rate and voltage). The characterization of microparticle formation involved the determination of droplet size and droplet size distribution using laser-diffraction method (Malvern 2000, Malvern Instr.) and image analysis (Nikon SMZ1000, Image J). To evaluate the microencapsulation efficiency, drug release and its dependence on the physicochemical environment (e.g. osmolality, pH) were investigated.

RESULTS: : A relatively low feeding rate and

alginate concentration favors optimal particle size distribution. The relationship between drug release kinetics and simulated environmental conditions can be established taking also the formulation parameters into consideration.

CONCLUSIONS: Based on our results optimal production parameters were determined for the preparation of caffeine-loaded alginate microspheres.

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POSTER SECTION 1E PHARMACOKINETICS, DRUG METABOLISM AND TRANSPORTERS

P1E-1

Challenges in equilibrium solubility measurements: difficulties in phase separation

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BACKGROUND: Knowledge of the physico-chemical parameters of drug molecules is essential in the estimation of their pharmacokinetic properties. Solubility is used to predict the absorption of orally administered drugs. Equilibrium solubility of drugs can be measured by different methods. The saturation shake-flask method is still the most frequently used procedure. The phase separation technique is a key part of this method. Three alternative techniques (sedimentation, centrifugation and filtration) can be used for the separation of the solid from the saturated solution before aliquots can be taken out for concentration measurement.

AIMS: The aim of the present study was to examine the effect of the filtration on solubility. The equilibrium solubility of hydrochlorothiazide, diclofenac sodium and papaverine hydrochloride was determined at different pH values using saturation shake-flask method. Hydrophilic and hydrophobic membrane filters as well as glass filters and analytical filter papers were applied.

RESULTS: In this study the effect of hydrophilic or hydrophobic type of membrane filters on the solubility results of ionizable molecules was proven. The selection of appropriate filter type requires the knowledge of the acid-base chemistry of the sample. Hydrophobic filter can be recommended for the filtration of the ionized form of the compound. For unionized drugs, hydrophilic filter can be recommended.

CONCLUSIONS: Sedimentation is the safest method for separation of the solid from the saturated solution. For non-clarifying, opalescent colloid solutions the centrifugation can be used. If filtration cannot be avoided, then it is essential that the proper filter type is selected. In this poster, a comprehensive, systematic investigation of the filtration and its influence on equilibrium solubility will be presented.

P1E-2

Study of interaction of reduced glutathione (GSH) with chalcone and some cyclic chalcone analogues

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BACKGROUND: Chalcones or 1,3-diaryl-2-propen-1-ones, are intermediary products and precursors of flavonoid biosynthesis. Both natural and synthetic chalcone analogues are proven to have various therapeutical activity such as cytotoxicity, anti-inflammatory, antitumor, and cancer-preventive properties. This class of compounds have shown preference in reactivity with thiols. In our earlier experiments some cyclic chalcone analogues showed a significant effect of reduced glutathione (GHS) status of Jukat T lymphocyte cells.

AIMS: To demonstrate the relationship between GSH-reactivity and anti-cancer properties of the investigated chalcones. To study stereochemistry of the reaction.

RESULTS: The investigated chalcones show an intrinsic activity towards GSH. This reversible Michael addition reaction yields maximum of two diasteromeric adducts in case of open chain chalcones or four ones in case of the cyclic analogues. The rate of the reaction depends on the proportion of deprotonated to protonated thiol function of GSH, as the deprotonated thiol is the more reactive form of it. Furthermore, reactivity depends on the ring size showing the open chain and the six-membered chalcones to be the most reactive. The rate of the reaction is also found to be depended on the nature of the 4′-substituents. The ratio of distereomeric adducts was found to be dependent on both

the pH and the ring size, as the mechanism and the stereochemical outcome of addition of the protonated and deprotonated thiol is different.

CONCLUSIONS: Chalcones possess intrinsic reactivity with GSH which can play role in development of their biological effects.

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P1E-3

Anticipation of absorption in dog using in vivo/ in vitro/in silico tools to prepare first in human studies

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BACKGROUND: Animal studies with support of in silico PBPK absorption tools are valuable data to build knowledge of physiological behavior of a formulated API to anticipate its pharmacokinetics in Human and to adapt the formulation when needed.

AIMS: This paper illustrates with six BCS II APIs examples how in vitro/silico/vivo studies conducted with a Beagle Dog model can be linked to rise understanding of the API behavior and propose an anticipation bioavailability (BA) in first in Human studies.

RESULTS: The first section presents for all compounds the correlation between observed BA in the pentagastrin-Dog (pgDog) model and BA predicted using in silico model built in GastroPlus v9.0 (SimulationsPlus, Inc), as well as the Human BA prediction. The second section illustrates the use of pgDog model to contribute to the formulation strategy, linked to API physical form and size. In a first example (compound A), an absorption increase obtained by reducing particle size was anticipated in silico and in vitro dissolutions on three batches with particle diameters varying from coarse (30µm) to micronized (3µm) ; the gain in AUC in pgDog was well correlated to this size reduction. The second example (compound B) points up the impact of surfactant into the formulation on the absorption of two physical forms (B1 & B2). Recommendation from in silico and in vitro tests was to include a surfactant to the granules of form B1, but not into form B2. In vivo PK profiles in fasted pgDog model confirmed the validity of this suggestion. Compound C example relates to the value of vitro dissolution on PK profiles interpretation and the importance of transit times in the GI tract.

CONCLUSIONS: Combination of in vitro/silico/vivo experiments on various compounds and formulation problematics around pgDog model allows foreseeing absorption in Human and helps designing first in man clinical studies by (1) orientating formulation options and (2) targeting dose adjustment.

P1E-4

Investigation of absorption and metabolism of ibuprofen in small intestine and bile in the rat

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BACKGROUND: *Per os* administered drugs are absorbed from the gastrointestinal tract, reach the liver through the *vena portae*, and get to the site of action by the systemic blood circulation. Ibuprofen typically excreted as ibuprofen-glucuronide, hydroxyibuprofen and carboxyibuprofen and both enzymatic and spontaneous processes can be involved in formation of them.

AIMS: *In vivo* investigation of intestinal absorption and metabolism of ibuprofen as well as appearance its metabolites in the small intestinal perfusate and in the bile, under physiologic and pathologic (diabetic) conditions. Development of HPLC method for quantitation of ibuprofen and its Phase I and Phase II metabolites. Analysis of non-enzymatic oxidative ibuprofen metabolites formed in the Udenfriend and the Fenton tests.

RESULTS: It was found that the enentiomeric ratio of the racemic ibuprofen slightly altered in the intestinal perfusate during the experiments. Under hyperglycaemic conditions the non-metabolized ibuprofen and its glucuronide conjugate decreased, however the quantity of the excreted oxidative metabolites significantly increased.

CONCLUSIONS: Hyperglycaemia increased the amount of oxidative metabolites that can be –

at least partly -the result of increased oxidative stress and/or elevated enzyme activities. Appearance of excess of the (S)-(+)-ibuprofen can be the result of active excretion of the metabolite.

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P1E-5

In silico modeling of salbutamol deposition and absorption following intravenous and inhalation administration in rats

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BACKGROUND: Contemporary trends in drug development highlight the utility of *in silico* tools for the prediction of drug bioperformance in humans and different animal species (1). Rat has commonly been used as animal model to study drugs absorption; however, examples of rat physiologically-based pharmacokinetic (PBPK) modeling for pulmonary drug delivery are rather scarce.

AIMS: The objective of this study was to develop an *in silico* model for the prediction of salbutamol deposition and absorption following intravenous and inhalation administration. GastroPlus™ software (v 9.0.0007, Simulation Plus, Inc. USA) and MPPD model (v 3.04, ARA, Inc. USA) were used for computer simulations. The necessary input parameters were obtained from literature or experimentally determined.

RESULTS: Drug-specific rat PBPK model was first developed and validated for intravenous administration, and further adjusted to simulate drug plasma profile after inhalation of experimental dry powder formulation. Modeling results were validated by comparing the simulated values with data from the *in vivo* study (2). The obtained results indicated that particle size, and concomitant regional lung particle deposition, are the key factors that influence salbutamol absorption after inhalation. Also, changes in rat physiological parameters notably influence the absorption profile of the inhaled drug.

CONCLUSIONS: *In silico* modeling of inhaled drug pharmacokinetics in preclinical species can facilitate the development of inhalation medicines. However, certain limitations such as incomplete knowledge of drug-related physiological mechanisms, along with uncertainties regarding the prediction of lung particle deposition, highlight the necessity for additional improvements in animal PBPK models.

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P1E-6

Semisolid self-microemulsifying drug delivery systems (SMEDDS): effects on pharmacokinetics of acyclovir in rats

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BACKGROUND: Acyclovir (ACV) is an antiviral agent whose absorption from gastrointestinal tract is slow, bioavailability is low (~ 15-30%), and half-life short ($t_{1/2}$ 2.5h) (1). One of the potential ways to improve pharmacokinetic parameters of ACV is developing semisolid self-microemulsifying drug delivery systems (SMEDDS) (2).

AIMS: Semisolid SMEDDS with ACV was prepared by measuring accurate quantities of oil (medium chain length triglycerides), surfactant (macrogolglycerol hydroxystearate), cosurfactant (polyglyceryl-3-dioleate), co-solvent (glycerol) and a viscosity modifier (macrogol 8000). The pharmacokinetic research was conducted on sexually mature white male Wistar laboratory rats (3). The animals were randomly divided into three groups and ACV was administered intravenously and orally in form of a suspension and semisolid SMEDDS, respectively. The animals were later treated orally with an aqueous solution of ACV, the self-dispersing formulation and ACV with the SMEDDS, during 7 and 21 days, respectively, in order to determine safety of semisolid SMEDDS by biochemical analysis.

RESULTS: ACV administered with semisolid SMEDDS can reach significantly higher maximum concentration in blood and has significantly shorter time reaching maximum concentration compared to the suspension of ACV (Cmax 247,31±28,7 ng/ml and 130,1±2,64 ng/ml; Tmax 23,33±5,16 min and 38,33±14,37 min, for the semisolid SMEDDS with ACV and the suspension of ACV, respectively). The bioavailability of the ACV is twice higher when it is in the form of the semisolid SMEDDS. Biochemical parameters doesn't show damage on function of liver and kidneys by administered formulation. CONCLUSIONS: Semisolid SMEDDS significantly improves pharmacokinetics of acyclovir and doesn't show damage on function of liver and kidneys.

CONCLUSIONS: Semisolid SMEDDS significantly improves pharmacokinetics of acyclovir and doesn't show damage on function of liver and kidneys.

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P1E-7

Pharmacokinetic study of fluorescently labelled hydroxypropyl-β-cyclodextrin

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BACKGROUND: Cyclodextrins are cyclic oligosaccharides, which consist of α-D-glucopyranose units. These molecules have a cylindrical shape, their outer surface is hydrophilic, but the inner cavity is hydrophobic. Nowadays cyclodextrins has an increasing importance as drug carriers, but hydroxypropyl-β-cyclodextrin is also used in the treatment of Niemann-Pick disease type C.

AIMS: The full characterization of biological properties of HPBCD has great significance. Our first aim was to test the safety of HPBCD by hemolysis test in correlation with the number of substitution groups. We also aimed to examine the pharmacokinetic properties of fluorescein-isothiocyanate labelled HPBCD (FITC-HPBCD) and evaluate its suitability for biological studies.

RESULTS: Our result showed that HPBCD has hemolytic effect just at extremely high doses. The degree of substitution of HPBCD molecules has a little effect on the hemolytic activity. FITC-HPBCD has fast elimination in BALB/c mice, but according to the pharmacokinetic model, tissue distribution could be also observed. The molecule was eliminated by the urine and the degree of tissue accumulation is insignificant at the end of the pharmacokinetic experiments. We studied the effect of FITC-HPBCD on endothelial cells in the third phase of the experiment. We showed, that endocytosis of FITC-HPBCD could be detected in HUVEC cells by fluorescent microscopy and flow cytometry.

CONCLUSIONS: In conclusion, FITC-HPBCD is a suitable fluorescent derivative for the pharmacokinetic analysis of HPBCD. The molecule can be used at high concentrations safely, and on the other hand the endocytosis in endothelial cells contribute to the better understanding of the distribution process.

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P1E-8

Evaluation of toxic profile of phenylethylamine entactogens by predicting on- and off-targets and by ADMET and QSAR studies

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BACKGROUND: A considerable research demonstrates that entactogens have serious toxic effects, both acute and chronic, that resemble those previously seen with other amphetamines. Among many others the four principal types of such serious toxicity are hepatic, cardiovascular, cerebral and hyperpyrexic.

AIMS: The aim of this study was to predict on- and off-targets as well as ADMET properties of selected phenylethylamine entactogens (n =

25) in order to get more insights in their toxic profile.

RESULT: The sodium dependent serotonin or dopamine transporters and trace amine-associated receptors were revealed by Swiss Target Prediction software as biological targets with the highest probability. Both, CYP inhibitor (1A2, 2D6) and CYP substrate properties (1A2, 2B6, 2C9, 2C19, and 2D6 and 2E1) have been predicted for majority of entactogens. QSAR studies, using computed molecular descriptors (LogP, M_r, TPSA, *V*) and topological indices (F, X, J, H, WW, W, Wp and Sz) with predicted ADMET properties computed by ADMET Predictor™ 8.1 (Simulations Plus, USA) revealed the most significant correlations between ADMET Risk *vs.* CYP Risk (R = 0.99), MLogP *vs.* TOX hERG (cardiotoxicity) and human plasma protein binding (R = 0.75 and R = 0.92, respectively).

Predicted ADMET risk were between 1 and 4 (codes 1A, 2C19, 2D6, Mu or Hp), CYP risk between 1 and 2.72 (codes 1A2, 2D6 and 2C19) and TOX risk between 0 and 3.45 with codes of mutagenicity (Mu) and hepatotoxicity (Hp). Mu was predicted for MDMEO or 1-(1,3-benzodioxol-5-yl)-*N*-methoxypropan-2-amine (14) and MDOH or 3,4-methylenedioxy-*N*-hydroxyamphetamine (**15**) while both Hp and Mu were predicted for MDCPM or 3,4-methylenedioxy-*N*-cyclopropylmethylamphetamine (18).

CONCLUSIONS: The results of this study revealed many unfavourable ADMET properties of evaluated molecules and MDCPM (**18**) as entactogen with the worst toxic profile.

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P1E-9

Diabetic conditions and drug vehicles alter drug metabolism

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BACKGROUND: Type II diabetes mellitus is a chronic disease, characterized by hyperglycemia and impaired metabolism. In diabetes, several metabolic pathways are altered, thus the biotransformation and pharmacokinetic of drugs can be influenced. According to epidemiological evidences, carotenoids are potent antioxidants and might have a protective role in chronic diseases. Because of their low solubility in water, cyclic oligosaccharides, cyclodextrins can be used to improve the aqueous solubility of carotenoids.

AIMS: We aimed to develop a method to investigate the effect of cyclodextrins (2-hydroxypropyl-β-cyclodextrin) and cyclodextrin-carotenoid complexes in streptozotocin induced animal model of type II diabetes mellitus with, or without the administration of insulin. Wistar rats were used in the experiments. During the method, the proximal jejunum of the diabetic and control rats is cannulated and perfused with the substances in Krebs-Tris buffer. Samples are collected from the intestinal perfusate and the bile. After the perfusion, different tissues (intestine, liver) were dissected and serum was collected for further investigations.

RESULTS: After the successful development of the method, the effect of the cyclodextrin and the cyclodextrin-carotenoid complex on the appearance of metabolites in the intestinal perfusate and bile, as well as the changes in the enzyme activities and drug transporter expressions in the tissues during treated or untreated diabetes can be studied. There is also a scope for the investigation of signaling pathways connected to inflammation during diabetes.

CONCLUSIONT: The applied method is suitable to investigate those alterations in treated and non-treated type I diabetes mellitus, which can influence drug metabolism, therefore may change the effect of agents. In addition, it can help to reveal the possible application of carotenoids in the treatment of diabetes in cyclodextrin-containing formulations.

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POSTER SECTION 1F DRUG DESIGN, SYNTHESIS AND CHEMISTRY

P1F-1

Chiral discrimination of fluoxetine enantiomers by capillary electrophoresis

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BACKGROUND: Fluoxetine (FLX) is a chiral selective serotonin-reuptake inhibitor, widely employed in therapy as an antidepressant. In chiral separation, capillary electrophoresis (CE) is considered to be an alternative for the more frequently used chromatographic techniques, with advantages related to high separation efficiency, low consumption of sample, reagents and chiral selectors and especially with the high flexibility in choosing and changing the chiral selector.

AIMS: FLX is used in therapy as a racemate, however stereospecificity associated with its interactions with the serotonin-reuptake carrier has been described and demonstrated; consequently development of analytical methods for its chiral separation become important for the pharmaceutical industry.

RESULTS:The study describes the development and optimization of a new CE method for the chiral discrimination of FLX using cyclodextrins (CDs) as chiral selectors. A complex screening of 11 native and derivatized, neutral and ionized CDs was carried out in order to establish the optimum chiral selector. As a result of this process, heptakis(2,3,6-tri-O-methyl)-β-CD was selected for enantiomeric discrimination. A factorial analysis study was performed by orthogonal experimental design in which six experimental factors were varied at three levels in order to optimize the separation method. The optimized method was successful for baseline separation of fluoxetine enantiomers within 5 minutes; the order of migration was established by spiking. The analytical performances of the method were verified in terms of repeatability, precision, linearity, sensitivity and accuracy. The method was applied for the determination of FLX enantiomers from pharmaceutical preparations.

CONCLUSIONS: A simple, rapid and cost effective CE method has been developed for the enantioselective determination of FLX enantiomers.
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P1F-2

Synthesis and biocompatibilty evaluation of new α-cyclodextrin derivatives

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BACKGROUND: The low solubility of drug candidates cause a major problem in pharmaceutical formulations, as the aqueous solubility is an indispensable criterion for appropriate bioavailability. Cyclodextrins (CDs) are widely studied organic host-compounds, and CDs have already been used as pharmaceutical excipients for solubility enhancement. The macrocycles' chemical structure allows their versatile modification, which eventuates changes not only in physicochemical characteristics, but in their effects on living organisms, as well. Thus, the biocompatibility evaluation of the derivatives is fundamental.

AIMS: Owing to the already performed assessment of numerous β-CD derivatives' biocompatibility, the aim of this research was to extend these experiments to commercially available α-CDs. They have been used less frequently, however several derivatives, which have not been tested yet *in vitro,* have the possibility of future pharmaceutical use. Their importance is also certified by their benefits in nanoparticle formation. We have been interested in concrete structure-toxicity correlations, thus alkyl ether α-CD derivatives were synthetized bearing increasing length alkyl chains, in different positions.

RESULTS: The cell viability and hemolysis tests

have allowed us to rank the α-CDs and to choose the safest derivatives, also to compare their toxic effects in different systems. The comparison of α- and β-CDs bearing the same chemical modifications highlighted the importance of the number of building units. [2] Important information has been evaluated regarding the connection between the cytotoxic effect and the number of free hydroxyl groups. Derivatives with long alkyl chains possess low solubility, which led us towards further chemical modifications. Sulfonation seemed to have beneficial impact on the biocompatibility.

CONCLUSIONS: Our research concludes, that the structural changes on the macrocyclic rings may have major impact on the biocompatibility. As the modification possibilities are practically unlimited, the evaluation of structure and activity cannot be avoided, facilitating the safest choice for further pharmaceutical use

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P1F-3

Preparation and antibacterial evaluation of some semisynthetic derivatives of teicoplanin and its hydrolysis products

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BACKGROUND: In a recent study, we have evaluated different derivatives prepared from one of the pseudoaglycons of the glycopeptide antibiotic, teicoplanin, for in vitro antibacterial activity. One derivative displayed noticeably higher activity against numerous vancomycin and teicoplanin resistant enterococci than the other compounds.

AIMS: The aim of this work was to study this particular molecule using well-known synthetic modifications in glycopeptide chemistry. We were interested to see if these transformations can influence the antibacterial activity in a similar way as it is described in the literature for this group of antibiotics.

RESULTS: 11 semisynthetic derivatives were prepared including the former compound. The transformations include the modification of the N-terminus by a diazotransfer reaction followed by a copper-catalyzed azide-alkyne click reaction to form a triazole derivative. This modification was carried out on teicoplanin, its two pseudoaglycons and on the aglycon. The C-terminus was also modified by PyBOP-mediated amide bond formation using 3-(dimethylamino)-1-propylamine and 3-(diethylamino)-1-propylamine. The compounds have been characterized either by MALDI-ToF, HPLC-MS, 1D-, 2D-NMR or all of these techniques. The measurement of antibacterial activites is in progress.

CONCLUSIONS: We have successfully synthesized and characterized all of the derivatives we have planned to prepare. Although the antibacterial activity of the molecules is not known yet, we will be able to present it on the conference along with structure-activity relationships.

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P1F-4

Novel synthesis of fluorinated 1,2,3,4-tetrahydroisoquinoline derivatives

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BACKGROUND: Due to their high biological potential, fluorinated organic compounds have increasing attention in organic and medicinal chemistry. The replacement of one or more hydrogen atoms by fluorine in biomolecules can generate changes in their physical, chemical and biological properties [1]. A number of isoquinoline derivatives exist in nature, and most of them have various biological activities [2].

AIMS: Taking into consideration of the high biorelevance of 1,2,3,4- tetrahydroisoquinoline alkaloids and of organofluorine scaffolds our aim was to develop a novel and efficient procedure for the access of fluorinated 1,2,3,4- tetrahydroisoquinoline derivatives.

RESULTS: The novel synthetic route started from indene and some substituted indene derivatives. They were oxidized with osmium tetroxide and these resulted vicinal diol derivatives which were carried out by sodium periodate mediated oxidative ring opening in order to get the corresponding diformyl intermediates. The unstable dialdehydes were subjected to reductive amination

with fluorinated amines resulting in fluor containing 1,2,3,4-tetrahydroisoquinoline derivatives.

CONCLUSIONS: A new convenient and efficient procedure has been developed for the synthesis of novel 1,2,3,4- tetrahydroisoquinoline derivatives, based on the C=C bond oxidative ring cleavage of indene and diversely substituated indene derivatives, followed by reductive ring closure of the diformyl intermediates using fluorinated amines.

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P1F-5

Catalytic deuterodehalogenation of haloarenes in continuous-flow

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BACKGROUND: The deuterium labelled compounds display widespread interest for scientists in many research areas. These compounds are used as internal standard in mass spectrometry, they are applied in the elucidation of biosynthetic pathways, they can be used to study reaction mechanisms. Nonetheless, deuteration can be used to increase metabolic stability of drugs.

AIMS: Continuous-flow (CF) technologies are of considerable current interest, since more efficient and selective reaction can be carried out in continuous systems than those for regular batch operations. Catalytic hydrogenation and deuteration reactions are known in CF systems, however the deuterodehalogenation reaction is practically unexplored. We aim to develop a CF deuteration technology with which selectively deuterated aromatic compounds can be gained

RESULTS: First a reaction parameter optimization was carried out. The results indicated that with regular supported Pd catalysts provide only law conversion rates even at harsh reaction conditions. In case of Pt catalysts, the partial saturation of the aromatic ring was observed. Thus we shifted our attention towards polymer-based spherical activated carbon (PBSAC), of which is a novel solid support for hydrogenation reactions. By a complete reaction parameter optimization full conversion was achieved with >95% deuterium incorporation. The reaction scope was extended to several haloarenes, including solely or multiply substituted chlorine and bromine substituted benzene derivatives. Iodine substituted derivatives poisoned the catalyst.

CONCLUSIONS: A selective and efficient CF catalytic deuterodehalogenation reaction was developed by the use of novel PBSAC supported Pd. Total conversions were gained a wide range of substances while high deuterium incorporation ratio was reached.

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P1F-6

Incubation time-, pH- and reagent ratio dependence of the product distribution in the Fenton reaction of salicylic acid

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BACKGROUND: Inflammatory and other pathological processes are often accompanied by oxidative stress. The reaction of reactive oxygen species with scavenger molecules can yield products that indicate their presence (and probably the underlying reason of their formation) both *in vivo* and *in vitro.* Salicylic acid is a good model compound for the examination of non-enzymatic oxidative transformation of phenolic compounds [1].

AIMS: We aimed to examine, how the change of the pH, the reaction time and the ratio of iron (II) to hydrogen-peroxide affects the quality and quantity of the products in the Fenton oxidation of salicylic acid.

RESULTS: The experiments were performed in at acidic (pH 3.0) and physiological (pH 7.4) pH with different iron (II) ion concentrations. The samples were analyzed at different time points of the incubations by a validated HPLC method. Similar to the *in vivo* results, in all incubates 2,3- and 2,5-dihydroxybenzoic acids were formed in the highest amount [2]. Furthermore, HPLC-MS analysis of the samples revealed presence of previously not identified monohydroxylated and a dihydroxylated salicylic acid derivative. The ratio of the reactants was found to have a significant

impact on the kinetics of the reaction and the ratio of the reaction products

CONCLUSIONS: Fenton reaction is a possible way of non-enzymatic oxidative transformation of phenolic compounds. Based on our *in vitro* results, the reaction can be a possible pathway of non-enzymatic oxidative biotransformation of phenolic xenobiotics under oxidative stress conditions.

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P1F-7

Concentration dependence of famotidine ^{1}H NMR chemical shifts in DMSO-d_6

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BACKGROUND: In our previous work [1] ^{1}H, ^{13}C and ^{15}N NMR spectral assignments of famotidine were clarified in DMSO-d_6. The results supported the predominance of extended conformers in this solvent in contrast to the previously supposed folded one. Furthermore, it was also revealed that besides the assignment, certain ^{1}H NMR chemical shifts also differed from previously published data [2], which raised the possibility of concentration dependence of ^{1}H NMR chemical shifts in DMSO-d_6, given the unknown solution concentration in Ref. [2].

AIMS: To explore the possible concentration dependence of ^{1}H NMR spectra in DMSO-d_6.

RESULTS: The ^{1}H NMR chemical shifts of the compound were measured in DMSO-d_6 solutions at 13 different famotidine concentrations ranging 0.29 mM to 2.96 M (1 g/ml). It was found that ^{1}H NMR chemical shifts of the compound were sensitive to concentration changes in solutions with concentrations exceeding ca. 15 mM, where the chemical shift values of all ^{1}H NMR signals showed an almost linear change. However, the concentration dependence differed significantly for the individual nuclei. Whereas the signals of the sulfonamide NH_2 protons and the "free" proton of the amidine NH_2 moiety suffered the largest chemical shift change with concentration (both 0.18 ppm), the smallest change (0.03 ppm) was observed for the other proton of the same amidine NH_2 group. This is in accordance with our previous finding namely the involvement of the latter proton in an intramolecular hydrogen bond with the neighboring sulfonamide group, resulting in its relatively low affinity to intermolecular interactions.

CONCLUSIONS: Based on the nature of the observed concentration dependence of the ^{1}H NMR chemical shifts, disintegration of famotidine polyassociates upon dilution can be assumed.

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P1F-8

Synthesis of 6-deoxy-l-talopyranoside-containing analogues of the anticoagulant pentasaccharide idraparinux

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BACKGROUND: Heparin has been employed in the medical practice since the late 1930's as a blood-anticoagulant. Enoxaparin, a low molecular weight oligosaccharides mixture (LMWH) drug, which made by the fractionation of heparin, have been among the world's ten most traded drug. The synthetic analogues, such as Arixtra and Idraparinux[(1,2)], are more effective than the heparin or Enoxaparin preparations but because of the complexity of their synthesis are not able to compete to the natural-based derivatives in the pharmaceutical market. The most problematic part of the synthesis of heparin derivatives is the preparation of the L-iduronic acid unit, this unique sugar does not occur in free form.

AIMS: Our goal was the substitution of L-iduronic acid with 6-deoxy-L-talopyranoside which has an essential flexible structure such as iduronic acid, and has an efficient and simple synthesis.

RESULTS: In our poster we will present the synthesis of a methylated, a partially methylated and a partially acetylated 6-deoxy-L-talopyranoside-containing idraparinux analogue pentasaccharides and the study of their anticoagulant activity.

CONCLUSIONS: We have successfully synthesized potentially active Idraparinux analogue pentasaccharides on shorter and more economical pathways. The anti-Xa activity measurements of these pentasaccharides are under way.

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P1F-9

Interaction of oligovalent alpha-L-fucopyranosides with recombinant Photorabdus asymbiotica lectin

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BACKGROUND: Photorabdus asymbiotica is one of the four recognized species of the Photorabdus genus, which consist of Gram-negative bioluminescent bacteria. It causes difficulty treatable locally invasive soft tissue infection and disseminated bacteraemic disease characterized by multifocal skin and skin tissues infection abscesses. A fucose/galactose-binding lectin (PHL) was identified from the bacteria and it was revealed that PHL has the ability to act as a host-cell recognizing agent. Therefore, PHL could be considered as a usable therapeutic agent.

AIMS: In order to produce potential glyco-inhibitors against PHL, alpha-L-fucoside containing mono-, di-, tri- and tetravalent glycoclusters were prepared.

RESULTS: Several oligovalent fucoclusters were synthesized using multivalent scaffolds by azide-alkyne click reaction. The interaction between fucoside derivatives and PHL was investigated by different biophysical and biological methods: not only ITC, SPR, STD-NMR, X-ray diffractometry were used but inhibition of agglutination and biofilm formation were also studied.

CONCLUSIONS: We have demonstrated that fucoclusters are able to inhibit the PHL lectin and the affinity for multivalent ligands reach up to nanomolar values. Moreover, we proved that oligovalent ligands are able to cross-link the PHL lectin. These results may find application in anti-adhesion therapy.

This work was supported by EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" project.

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P1F-10

Development of HPLC method for estimation of 18β-glycyrrhetinic acid phytosomes in carbomer based hydrogels

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BACKGROUND: 18β-glycyrrhetinic acid phytosome® (GAP) is a complex of the highly pure extracts of *Glycyrrhiza glabra* rhizomes (27-31%) and phosphatidylcholine, with antiinflammatory, antiirritant and soothing effects and well tolerated for topical application in hydrogels (1,2). In general, the ingredients of plant origin are hygroscopic and prone to oxidation (1), thus formulation requires careful consideration of their stability within the specified vehicle and under the defined storage conditions.

AIMS: The study aimed to develop the HPLC method for determination of the GAP content in the carbomer based hydrogels.

RESULTS: The hydrogel with 1% of GAP was prepared by using Carbopol®Ultrez 10 (a gelling agent) (0.5%), sodium hydroxide (a neutralizing agent) (0.4%), glycerol (a humectant) (10%), Sepicide® HB (a preservative) (1%), and water (up to 100%). Chemical stability of GAP was evaluated by the developed and validated HPLC method. The chromatographic conditions were: Hypersil C_{18} 150 ´ 4.6 mm, 5 μm, λ=220 nm, column temperature 30°C, flow rate 1 mL min^{-1}, and mobile phase: acetonitrile - 15 mM CTAB (20:80 v/v), pH 2.5. Surprisingly, the content of GTP after 3 months storage under ambiental conditions was 190.35%. It was observed that although at the end of the third month the consistency was thicker compared to initial, the sample was homogeneous. Moreover, the centrifugation test could not indicate the syneresis phenomenon and the results of rheological characterization indicated that the hydrogel appearance was affected by shrinkage

due to water evaporation (3). Therefore, the stability of the investigated sample concerned satisfactory, while the observed apparent increase in the GAP load was related with the decrease of the hydrogel mass due to evaporation loss.

CONCLUSIONS: On the basis of the obtained results it has been concluded that the developed and validated HPLC method was suitable for chemical stability assessment of GAP loaded in the hydrogel type formulations.

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POSTER SECTION 1G PRECLINICAL DRUG RESEARCH

P1G-1
Endocannabinoid signalling in migraine

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BACKGROUND: At the beginning of the last century, the extracts of the *Cannabis Indica* plant were one of the suggested treatment of migraine. This branch of the traditional medicine led to discover the endogenous cannabimimetic compounds, the endocannabinoids.

AIMS: The purpose of this review was to determine the relevance of endocannabinoid system (ECS) in the evolution of migraine by using scientific literature.

RESULTS: Previous studies demonstrated the location of cannabinoid receptor 1 (CB1) in pain processing areas like trigeminal system, periaqueductal grey matter, thalamus and others. In addition, animal studies reported the influence of AEA (anandamide), one of the best characterized CB1 receptor endogenous agonist, on the activation and the sensitization process in the trigeminal system. Some clinical studies underlie the phsysiological analgesic effect of ECs, next to its other regulatory roles in stress response regulation, appetite control and motor learning. In addition, reduced concentration of AEA was measured in migraineurs' blood and increased activity of AEA hydrolase and AEA transporter was detected in female migraineurs, but not in males. This latter finding possibly explain the higher prevalence of migraine in women.

CONCLUSIONS: In patients suffering from migraine, an edocannabinoid system impairment is hypothesized but the exact nature of this is unkwon yet. Although, the ECS is an interesting avenue of antimigraine drug developement, there is still no medication on the market today that regulates ECS.

ACKNOWLEDGEMENT: The study was supported by Hungarian Brain Research Program – Grant No. KTIA_NAP_13-2-2015-0001 (MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group) and by the Hungarian Academy of Sciences (MTA-SE Neuropsychopharmacology and Neurochemistry Research Group).

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P1G-2
Biocompatibility investigation of pharmaceutical excipients

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BACKGROUND: Liquid pharmaceutical preparations are vulnerable to microbiological contamination and thus, must contain a broad-spectrum antimicrobial agent which can prevent the reproduction of microbes, but these compounds have a significant cytotoxicity on human cells as well. Additionally it is important, what salt or derivative of the specific preservative has been used and there are other pharmaceutical excipients like surfactants, which have their own and synergetic cytotoxic attributes in different pharmaceutical preparations.

AIMS: Based on these effects we aimed to create an experiment to determine the biocompatibility of preservatives and other excipients which are generally used in pharmaceuticals. We both wanted to test them on their own and in combinations. Also we tested different paraben derivatives, salts

of sorbic and salicylic acid to investigate the chemical structures' effect on cell-damage. The other tested excipient groups were the thickener polymers and various surface-active agents to observe the biocompatibility of a real pharmaceutical compound which contains multiple excipients apart from the active substance.

RESULTS: In order to avoid the animal experiments, we used human cell lines of Caco-2 and HaCaT. We determined the cytotoxicity with MTT-assay and RT-CES. The surfactants greatly increased the cytotoxicity of preservatives, but in some cases, the thickening agents could decrease this effect. Also, the different preservative derivatives acted in a different way given on what other excipients were in the test system and their dissociations in the given pH values.

CONCLUSIONS: Overall, we can state, that no general IC_{50} value can be measured in case of pharmaceutical preservatives. The other components of pharmaceuticals, like surfactants and thickeners can greatly modify the preservatives' biocompatibility. During formulation, the cytotoxicity must be assessed and cannot be calculated based on previous researches.

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P1G-3

Abdominal detection of uterine electromyographic signals in pregnant rat: strong correlation with mechanical contractions

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BACKGROUND: Premature labour is the major contributor to perinatal mortality and morbidity. There is a need for sensitive, reliable method to detect and follow the myoelectric activity of the pregnant uterus.

AIMS: Our aim was to develop an electromyography method for pregnant rat myometrium in vivo and to separate them from other smooth muscle signals to predict premature contractions or other disorders.

RESULTS: The frequency of the electric activity was characterized by cycle per minute (cpm), the magnitude of the activity was described as power spectrum density maximum (PsD_{max}). In anaesthetized rats, the frequency of the pregnant uterine activity was found at 1-3cpm that falls within the same range than that of caecum.[1] Oxytocin (1μg/kg) increased by 25-50%, while terbutaline (50μg/kg) decreased the PsD_{max} by 25-40% measured by silver thread or subcutaneously placed disk electrodes. We found a strong positive correlation between the alterations of PsD_{max} values and the strain gauge sensor-detected mechanical contractions (AUC). The GI specific compounds (neostigmine-atropine) mainly affected the cecal activity, while myometrium specific drugs (oxytocin-terbutaline) influenced the myometrial signals only.[2]

CONCLUSIONS: The myoelectric activity of pregnant rat myometrium is measurable from the abdominal surface and well-characterized by cpm value. The PsDmax values express the intensity of contractions and reflect contracting and relaxing effects in the myometrium. The overlapping myometrial and cecal myoelectric signals are not separable, but they can be distinguished based on their different activities and pharmacological responses. Thus the early signs of contractions can be detected and labour can be predicted in a fast and sensitive way.

The work was supported by the project PIAC_13-1-2013-0201, National Research, Development and Innovation Office, Hungarian Government.

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P1G-4

Possible connection between heme-oxygenase-1/CO system and autophagy in cardiomyocytes

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Several group have demonstrated that separately the increased activity of heme-oxygenase-1/CO system and autophagy could protect the myocardium against ischemic events. However, it is still not clear whether a connection between HO-1/CO system and autophagy processes exists in the myocardium.

In the current study we aimed to examine the possible connection between the two systems. H9c2 cardiomyoblast cells were treated with different dose of hemin or cobalt-protoporphyrin IX (CoPPIX) or vehicle (20mM NaOH solution) for 24-h. After the treatment of the cells cytotoxicity was measured by MTT assay. Furthermore, staining was carried out to determine the alterations in cell size. To study the autophagic process CytoID staining was carried out and cells were studied by fluorescence microscope. Moreover, Western blot analysis was performed to analyse the level of HO-1, certain autophagy related proteins and apoptosis markers.

We have detected a slight decrement in cell viability in the hemin and CoPPIX treated groups, respectively, which may indicate a toxic effect of high concentration of heme-oxygenase-1 inducers. The cell size did not alter. As it was expected a robust induction of HO-1 were detected with both of inducer. An enhanced number of autophagosome were detected by CytoID staining, and elevated level of LC3B-II was found in the highest hemin and CoPPIX treated groups.

Taken together, our results show that, there is a connection between HO-1/CO system and autophagy process, but further experiments needs to be carried out to precisely understand the nature of the connection.

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P1G-5

Investigation of the endocytosis and its cellular effects of beta-cyclodextrin derivatives on intestinal epithelial cells

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BACKGROUND: Cyclodextrins are widely used excipients for increasing water solubility, delivery and bioavailability of lipophilic drugs. Using fluorescent cyclodextrin derivatives we showed previously, that cyclodextrins are able to enter Caco-2 intestinal cells by endocytosis, but the different fluorescent labelling have not been compared on the same cyclodextrin derivative. On the other hand the consequences of the cellular internalization of cyclodextrins have not been revealed yet.

AIMS: Our aim was to compare the cellular internalization of fluorescein and rhodamine labeled hydroxypropyl (HPBCD) and randomly-methylated beta-cyclodextrins (RAMEB). We also aimed at examining the effect of these cyclodextrins on NF-kappa B pathway and autophagy on Caco-2 cells.

RESULTS: Using fluorescent microscopy and flow cytometry we tested the endocytosis of the fluorescent cyclodextrins. Both fluorescein and rhodamine labelled derivatives are able to enter the intestinal Caco-2 cells by endocytosis in a comparable manner. Cooling almost perfectly inhibited endocytosis, while the application of rottlerin inhibited significantly the uptake of cyclodextrins. We investigated the possible activation of NF-kappa B pathway, which is important in regulating cellular responses. Cyclodextrin pretreatment did not activate the translocation of the p65 subunit of NF-kappa B heterodimer into cell nuclei both in cell monolayers or undifferentiated cells. After HPBCD and RAMEB treatments the presence of autophagosomes is detectable on fluorsecent microscopic images, similar to control samples.

CONCLUSIONS: The type of fluorescent labelling does not influence the internalization of HPBCD and RAMEB cyclodextrin derivatives. FITC and rhodamine conjugates showed similar intracellular localization. The endocytosis of cyclodextrin does not activate NF-kappa B pathway, while the examination of autophagy induction requires further quantitative analysis.

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P1G-6

The role of circulating extracellular vesicles on human in vitro osteoclastogenesis

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BACKGROUND: Extracellular vesicles (EV) are subcellular sized signalosomes which carry wide variety of biomolecules and are present in various biological fluids. Exosomes (EXO), the smallest EVs, originate from the endosome. Microvesicles (MV) are plasma derived vesicles. EVs may alter the recipient cells' functions and will become novel delivery systems in therapy in the future.

AIMS: Our objectives were to investigate the role of blood-derived EVs on the human *in vitro* osteoclastogenesis and to characterise the serum EV profile of healthy donors, rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients. RA is a chronic autoimmune disorder that primarily affects small joints, PsA is a long-term inflammatory arthritis that occurs in patients with psoriasis.

RESULTS: Microvesicles did not alter the number of mature osteoclasts. By contrast, exosomes significantly ($p < 0.01$) inhibited the osteoclast differentiation of the healthy and RA donor-derived monocytes *in vitro*, but not those of the PsA patients' monocytes. EXO and MV treated osteoclast samples contained less cathepsin K (CTSK) compared to the untreated osteoclast samples, studied by Western Blot method. H- and RA-derived EXOs expressed significantly more RANK compared to PsA plasma-derived ($p < 0.05$) EXOs measured by flow cytometry. H and RA plasma-derived MVs did not carry RANK in contrast to PsA plasma-derived MVs.

CONCLUSIONS: Our present data suggest that EVs profoundly regulate osteoclastogenesis. The plasma profile of EVs is altered in different inflammatory arthropathies.

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P1G-7

Biocompatibility examination of 3D printed implants

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BACKGROUND: 3D printing is a modern method which can be used in numerous areas for example in the industrial pharmacology. With the use of 3D printing complex and personalized products can be made on-demand. The examined implants are manufactured at the University of Claude Bernard, Lyon.

Biocompatibility is a very important question through the development because implanted devices must be biologically compatible with the tissues. The aim is to maximalise the benefit and minimize the risk. [1.]

AIM: Our aim was to determine the biocompatibility of the implants. Biocompatibility can be examined by biofilm formation and MTT cell viability test. Another aim is to gain information about the structure of the implants. Material structure can be examined by PALS (positron annihilation lifetime spectroscopy) this results will determine the free volume in the implants.

RESULTS: Nearly twenty samples were examined with MTT assay and based on the results all of the samples are suitable for further examinations but a cytotoxic ranking can be set up: the lowest toxicity in the case of PLA, then PET and finally PMMA.

Based on biofilm formation we can select the best implants which are appropriate to further examinations. A biofilm formation ranking can be set up: lowest in the case of PLA, then PET, different PMMAs, PLA one and two. Nylon is inadequate to further examinations.

PALS method determined the free volume in the implants which give us information about the further applicability of the samples.

PLA samples have given the best results and this is advantageous because it is a biodegradable polymer.

CONCLUSION: By determining the data and analyzing the results information can be provided

to the University of Claude Bernard to produce the most appropriate implants. Based on this the plan can be made for scale enlargement.

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P1G-8

Possible connection between the anti-aging klotho protein and autophagy

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BACKGROUND: According to the WHO, the average age of the population is increasing. Age is considered as main risk factor for the common diseases including cardiovascular disease and cancer in the developed countries. Several studies show that autophagy plays an important role in aging. Numerous studies revealed that autophagy decreases with aging.

AIMS: In this study we have investigated the connection between autophagic process and the level of klotho protein.

RESULTS: To induce the klotho protein aged mice were treated with rapamycin. Thereafter the organs were isolated. The expression levels of anti-aging klotho protein and autophagic, apoptopic proteins such as LC3B-II and p62 were evaluated by Western blot. We have noticed decreased lifespan and body weight at the control group compared to mice exposed to rapamycin, where the extended lifespan suggests that klotho functions as an anti-aging protein. We have investigated that the expression level of the klotho increased in most of the organs, especially in the kidney. Furthermore, a decreased p62 protein level was found in the treated group, which is involved in the regulation of apoptosis and autophagy.

CONCLUSIONS: Taken together our results suggest that in case of rapamycin induced klotho protein autophagy is increasing, which may help to reduce damaged protein organelles. Acknowledgements: OTKA-PD-111794, TÁMOP 4.2.4 A/2-11-1-2012-0001, GINOP-2.3.2-15-2016- 00043, EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" project.

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P1G-9

Time course of gene expression changes in trigeminal neurones and peripheral blood mononuclear cells in a rat orofacial pain model

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BACKGROUND: The origin and precise pathomechanism of migraine are still being debated. The headache and the referred hyperalgesia and allodynia on the face suggests that there is an underlying trigeminal nociceptor sensitization. Modelling complex mechanisms and symptoms accompanying primary headache disorders in animals are challenging, however, a possible approach to study the mechanisms involved in the pain is to adapt inflammatory pain models to the orofacial area.

AIMS: We aimed to investigate gene expression changes in trigeminal ganglia (TRG), central trigeminal nucleus caudalis (TNC) and peripheral blood mononuclear cells (PBMCs) evoked by Complete Freund's Adjuvant (CFA) induced peripheral inflammation in rats.

RESULTS: 253 differentially expressed genes were found between CFA-treated and contralateral TRG samples 7 days after CFA injection. The mRNA expression changes of G-protein coupled receptor 39 (Gpr39), kisspeptin-1 receptor (Kiss1r), Lkaaear1 and Otoraplin were validated. They were most upregulated on day 3 in TRGs of the CFA-treated side. CFA induced significant orofacial mechanical allodynia in one day with a maximum on day 3. This correlated with patterns of neuronal (FosB), microglial (Iba1), and astrocyte (GFAP) activation markers in both TRG and TNC, and surprisingly in PBMCs. In TNCs, gene expression changes similar to TRGs were observed but Kiss1r transcripts were not significantly altered.

CONCLUSIONS: The genes revealed by our study may participate in the cascade of events resulting in the sensitization underlying migraine headache and the accompanying facial allodynia, thus may become potential targets for drug development. The finding that there are corresponding mRNA changes in PBMCs is an intriguing result that might lead to the identification of novel biomarkers.

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P1G-10

Altered behavior, learning and memory functions in somatostatin receptor subtype 4 gene-deficient mice

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BACKGROUND: Somatostatin is an inhibitory neuropeptide regulating a variety of functions both in the peripheral and central nervous systems. Our team has previously discovered that among its five G_i-protein-coupled receptors, somatostatin receptor subtype 4 (sst_4) mediates anti-inflammatory, analgesic and antidepressant effects without endocrine actions.

AIMS: The aim of our study was to examine the role of the sst_4 receptor in behaviors related to learning and memory processes (Y-maze, Open Field, Radial-Arm Maze and Novel Object Recognition Test) using gene-deficient ($sst4^{-/-}$) male and female mice, and their wild-type ($sst_4^{+/+}$) counterparts.

RESULTS: Female $sst_4^{+/+}$ mice time spent significantly longer time in the middle of the OFT than their male wild-type counterparts, but the number of visited arms and arm combinations in the Y-maze was not different. Furthermore, they visited, repeated and missed significantly more arms, but found the same amount of rewards in the RAM, and they also spent significantly longer time by exploring the novel object in NOR compared to male wild-types. Female $sst4^{-/-}$ mice visited and repeated less arms in both mazes, but they found the same amount of rewards and spent more time to explore the novel object in NOR compared to their wildtypes. In contrast, male $sst_4^{-/-}$ mice found significantly less rewards in the RAM and they were less interested to explore both objects in the NOR compared to their wild-types.

CONCLUSIONS: Based on these data, female mice showed greater spontaneous locomotor activity, less anxiety, worse long-term learning ability and exploration skills than males. Sst_4-deficiecy resulted in faster short-term learning in females, but worse exploratory behaviour in both sexes. These results suggest that sst_4 is an interesing complex regulator of behavior and cognitive functions under healthy conditions, but further investigations are needed to determine its role in memory deficits during aging or other pathological conditions.

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P1G-11

Transfer of Complex Regional Pain Syndrome to mice via human autoantibodies is mediated by interleukin-1-induced glia cell activation and central sensitization

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BACKGROUND: Complex Regional Pain Syndrome (CRPS) is a multifactorial disease characterized by severe, persistent pain accompanied by abnormal hypersensitivity, swelling and autonomic alterations of the skin. Although the ethiology is unknown, immune response against sensory nerve-derived antigens and complex neuro-immune interactions are suggested to be involved in the development of this disease.

AIMS: Our aims were to investigate the effects of the recombinant IL-1 receptor antagonist anakinra and corticosteroid prednisolone in the novel passive-transfer-trauma CRPS model. Small plantar skin-muscle incision to mimic the small injury was performed in female C57Bl/6 mice. Animals were treated with serum-IgG from CRPS patients or healthy volunteers. Anakinra or prednisolone was also administered, saline-treated groups served as controls. The volume of the hindpaw was measured by plethysmometry, the

mechanonociceptive threshold by dynamic plantar aesthesiometry. The neutrophil/macrophage myeloperoxidase (MPO) activity by luminescence in vivo imaging, inflammatory cytokines by immunoassays, Iba1 microglia and GFAP astrocyte markers by immunochemistry in pain-related brain regions.

RESULTS: Following CRPS IgG injection we measured significantly increased incision-induced swelling and MPO activity, but more pronounced enhancement and prolongation of hyperalgesia was observed compared to healthy IgG. CRPS IgG significantly increased the density of both Iba1 and GFAP immunopositivities. Anakinra treatment abolished the CRPS IgG-evoked increased hyperalgesia and glia activation, but not the peripheral inflammatory alterations. Prednisolone affected neither edema nor hyperalgesia, and surprisingly did not influence the MPO activity and cytokine production.

CONCLUSIONS: These results suggest that glia-mediated central sensitization mechanisms play a crucial role in the enhanced and prolonged hyperalgesia in CRPS. Anakinra is likely to act centrally by inhibiting IL-1-mediated neuroinflammatory pathways and might open new perspectives for its use in CRPS as a novel indication.
KTIA_NAP_13-2014-0022 (PTE-NAP B); Pain Relief Foundation; EFOP-3.6.1-16-2016-00004; GINOP-2.3.2-15-2016-00050 –383 PEPSYS és GINOP-2.3.2 STAY ALIVE

P1G-12

Evaluation of fibroblast cell growth on 3D printed polylactic acid based human auricular model in the presence of cyclosporine and co-enzyme Q10 loaded solid lipid nanoparticles

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BACKGROUND: Tissue engineering is an interdisciplinary field which applies the principles of engineering and the life sciences toward the development of biological substitutes [1]. Recently 3D printing have been successfully used to fabricate complex scaffolds constructions [2]. These scaffolds provide structural support as well as promoting attachment, proliferation, and differentiation with the ultimate goal of yielding functional tissues or organs.

AIMS: The aim of this study was to use a commercial 3D printer and combine them tissue engineering techniques together for developing human auricular models. For this aim fibroblast cell growth on 3D printed PLA based human auricular model in the presence of cyclosporine and coenzyme Q10 loaded solid lipid nanoparticles (SLNs) were evaluated. The effect on cell proliferation was investigated.

RESULTS: MTT assay was performed by 3T3 dermal fibroblasts and a significant poliferation was seen on 3D printed PLA auricular model. After determining the suitability of PLA, SLNs were added in culture media. Addition of nanoparticles did now show a cytotoxic effect. The combination of nanoparticles were also suitable in terms of cytotoxicity.

CONCLUSIONS: In this study it was shown that 3D printing, solid lipid nanoparticles and tissue engineering techniques can easily be used together for human auricular defects.

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POSTER SECTION 1H
NATURAL PRODUCTS

P1H-1

Determination and comparison of phenolic compounds of medicinal plants and veterinary herbal medicines

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BACKGROUND: Phenolic compounds from medicinal plants have several biological effects such as anti-inflammatory and antioxidant properties which were well-known in phytotherapy and ethno-veterinary practices too.

AIMS: We determined by screening the total phenolic and flavonoid compounds from thirteen veterinary products and from fifteen medicinal plants occurred in these products [1,2]. For flavonoids we used the total and C-O glycosides deter-

mination. The polyphenols and flavonoids were determined by colorimetric methods. For these determination we prepared from investigated medicinal plants methanolic, methanol and water (1:1), and ethanolic (70°) extracts. The mentioned compounds were determined directly from liquid veterinary products.

RESULTS: The total polyphenolic (7 - 54 mg gallic acid equivalent/100 g product and 4 - 44 mg gallic acid equivalent/100 g dry weight plant) and flavonoid concentration (5 - 21 mg quercetin equivalent/100 g product and 4 - 39 mg quercetin equivalent/100 g dry weight plant.) were with highest concentration from ethanolic extracts. The C-O flavonoid glycosides concentration showed lower value with these colorimetric determination (1.1 - 1.7 g hyperoside/100 g product and 1.2 –5.7 g hyperoside/100 g dry weight plant).

CONCLUSIONS: We observed the great variability of phenolics and flavonoids compound. There are a wide variety of extraction methods for determination of phenolics and flavonoids. The polyphenols have the potential to be integrated in these veterinary products and used to promote animal health.

ACKNOWLEDGEMENTS: The research was supported by the University of Medicine and Pharmacy of Tîrgu Mureș and SC Promedivet SRL, internal research grant number 17972/07.12.2016.

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P1H-2

Antibacterial effect of cinnamon bark, clove, thyme and peppermint oil against respiratory tract pathogens

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BACKGROUND: Essential oils (EOs) have been widely used for medicinal and cosmetic purposes. Nowadays in the health care EOs and their components are becoming increasingly popular as naturally occurring antimicrobial agents.

AIMS: Thus, the aim of this study was the evaluation of antimicrobial properties of cinnamon bark (*Cinnamomum verum* J. Presl.), clove (*Syzygium aromaticum* (L.) Merr. and Perry), peppermint (*Mentha x piperita* L.), and thyme (*Thymus vulgaris* L.) EOs including their main components against respiratory tract pathogens especially *Haemophilus influenzae* (DSM 4690) and *H. parainfluenzae* (DSM 8978).

RESULTS: The chemical composition of the EOs was measured with gas chromatography – mass spectrometry (GC-MS). Thin-layer chromatography – direct bioautography (TLC-DB) and broth dilution (BD) method were used for the *in vitro* detection. In the case of TLC-DB the oils were diluted in absolute ethanol (20 mg/mL). An aqueous solution of MTT (3-[4,5-dimethyl-thiazol-2-yl]-2,5-diphenyltetrazolium bromide) was used for the visualization of inhibition zones (expressed in diameter, mm). Standards of the main components were also involved in the experiments. 5% emulsion was prepared from each EO with 10% solution of Tween 80 for the BD technique. Detergent control was also prepared. All measurements were made in triplicate. The minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values of the EOs were expressed in mg/mL. In TLC-DB cinnamon oil (19.5 mm) and cinnamaldehyde (23 mm) were the most active agents against both bacteria. In comparison with peppermint oil (8 mm) EOs of thyme and clove were more effective (11-12.5 mm). In BD assay cinnamon bark oil produced the lowest MIC value (0.06 mg/mL) which met the results of the other *in vitro* technique. In contrast with the TLC-DB thyme oil showed better activity than clove and peppermint in the BD assay.

CONCLUSIONS: To the best of our knowledge, we performed TLC-DB with *Haemophilus* species firstly. In our further studies, we are planning to extend our research including other pathogens and to determine the mode of action of the effective oils in biofilm-formation method.

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P1H-3

The antiviral properties of chamomiles on lentivirus

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BACKGROUND: Lentivirus (i. e. HIV) is a genus of retroviruses, which are spread worldwide and cause serious diseases (i.e. AIDS). German chamomile (Chamomilla recutita (L.) Rauschert) is one of the most popular medicinal plants in the world and has been used in traditional medicine as an antimicrobial, antiseptic, anti-inflammatory medicine etc. Our previous studies have shown that its chemical composition is similar to pineapple weed (Chamomilla suaveolens (Pursh) Rydb.).

AIMS: The aim of our study was to analyse the antiviral properties of the herbal extracts of the two species of chamomiles on HIV-1 based viral like particles (VLP) expressing Gaussia luciferase (Gluc) as a quantitative reporter.

RESULTS: For the experiments, 70% ethanol extracts of both chamomiles were prepared. First, the maximal noncytotoxic concentrations (dilutions) of the extracts were determined using the tetrazolium dye MTT cell viability assay. The antiviral properties of chamomiles were analysed using ViraPower Lentiviral Expression System. Herbal extracts were preincubated with the VLPs, and were present in the infectious medium during the infection time as well as in the growth medium during 48 h after infection. The antiviral effect was determined by measuring the activity of Gaussia luciferase from infected cell lysates, which was normalized to the total cellular protein concentration. Both chamomiles demonstrated inhibitory effect on the replication of HIV-1 based VLPs. The experiment with serial dilutions of the extracts downward of the maximal noncytotoxic dilution showed that the inhibitory effect is dose-dependent.

CONCLUSIONS: Both herbal extracts showed antiviral properties on HIV-1 based VLPs. Further analysis with essential oils and water extracts of chamomiles are being carried out at present.

P1H-4

Effects of different parameters of herbal tea preparation on active compounds

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BACKGROUND: One of the oldest and most popular methods for preparation of herbal extracts is the preparation of a tea. However, some questions have arisen: How do different parameters of preparation influence the amount of active compounds in a tea? Do we prepare our teas correctly today?

AIMS: To answer these questions, we examined three commercially available drugs official in the Ph. Eur., namely Silybi mariani fructus, Uvae ursi folium, and Rosae pseudofructus.

RESULTS: For preparation of water extracts, we used three different temperatures and periods of time (hot water for 5 min, room temperature for 2 hours, and room temperature for 10 hours) given by the manufacturers on the labelling. HPLC was used for determination of silybinin, arbutin, and hydroquinone contents, and spectrophotometric methods were used for determination of total tannin and vitamin C contents. As expected, nearly no silibinin could be detected in the teas of Silybi mariani fructus, and the vitamin C content of Rosae pseudofructus was the highest in samples extracted at room temperature for 10 hours. Indeed, the arbutin and hydroquinone content of Uvae ursi folium increased with the longer time of extraction, but the tannin content (responsible for side effects) also increased.

CONCLUSIONS: To sum up, it is surprising that Silybi mariani fructus is commercially available for tea preparation, however, its hepatoprotective compounds are not water soluble. Contrary to the recommendation, 10-hour soaking is not appropriate for Uvae ursi folium, because tannin content will also increase. However, it is well-known, that the best method for extraction of vitamin C from Rosae pseudofructus is the soaking for several hours at room temperature, most of the patients use hot water for 5-10 min in our accelerated lifestyle, thereby reducing the effectiveness of the therapy.

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P1H-5

Investigation of topical formulations containing silybum marianum extract against UVB-induced oxidative stress in guinea pig and on HaCaT keratinocytes

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BACKGROUND: Plants with high amounts of antioxidants may be a promising therapy for preventing and curing UV-induced oxidative skin damage. The topical application of Silybum marianum extract has been already reported to have protective effects against UVB-induced skin damage [1]. However, the low solubility and low bioavailability of silymarin limits extensive topical applicability [2]. Different compositions of silymarin creams were formulated and the diffusion of active substance was determined with Franz diffusion cell. Antioxidant enzyme activities (glutathione peroxidase, GPX; superoxide dismutase, SOD; catalase, CAT) were determined, lipid peroxidase tests were also performed and heme-oxygenase (HO-1) enzyme activity was measured on HaCaT keratinocytes and in skin tissue of guinea pigs in the pre and post-treatment of silymarin creams against UVB irradiation.

AIMS: The aim of the present study was to design new hydrophilic topical formulations containing Silybum marianum extract and to show the antioxidant activity of creams against UV-induced oxidative stress in guinea pig model and HaCaT cells.

RESULTS: The results of in vitro membrane diffusion studies justified that Transcutol – which also helped in the dissolution of silymarin powder- with sugar-ester type emulgents elevated the amount of active substance across the diffusion membrane. The pre and post-treatment of creams containing silymarin powder in dissolved form showed sufficient antioxidant activity against UV-induced oxidative stress in guinea pig model and HaCaT cells.

CONCLUSIONS: Significance of post-treatment is outstanding because silymarin creams may provide potential therapy against skin damages.

This work was supported by EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" project.

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P1H-6

New perspectives on the antiaging dermocosmetic use of Salvia officinalis volatile oil

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BACKGROUND: Reserchers` efforts to find active anti-aging substances focus on accepted and desirable species of plants, although synthetic peptides may be more targeted in this regard. Salvia officinalis is not only known in pharmacognosy but also recently researched as a colagen-syntetisuing and antiglycation species. In theory, blocking the dermal collagen glycation would provide elasticity and youthfulness to the skin.

AIMS: The study ainm s to evaluate by corneometry, in vivo, on volunteers, the antiaging effect of a pharmaceutical form for cutaneouse use containing Salvia officinalis oil

RESULTS: The values obtained in corneometry, separately for photoaging and chronoaging, were statistically processsed with the StatPad application. Analyzing the dispersion diagrams and the values of the correlation coefficeients, it can be concluded that the use of the preparated creams containing Salvia officinalis oil leads to an increase in the hydration degree both in the cases of chronoaging and in the cases of photoaging as compared to the whitness sample. In both situations there is a substantial improvement in the hydration of the skin. This confirms also the traditional use of sage oil for beauty and skin rejuvenation in certain geographic regions.

CONCLUSIONS: The encouraging results of this research deserve to be continued with cutometry and skin-visiometry

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P1H-7

Extraction, purification and cristallisation of rebaudioside A, a sweetener from Algerian culitvated Stevia rebaudiana

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BACKGROUND: Diabete by its constant increase became the century desease, in Algeria mostly 12 % of the population is touched by this plague. it is important for patient to be able to use medicines and beverages with a sweet taste but without any health risk. By cultivating Stevia rebaudiana, a sweet plant form Paraguay in Algeria, the sweetener rebaudioside A could be obtained and accessible for the common patient.

AIMS: The Aim of this study is to optimize the extraction process (infusion) of rebaudioside A from Stevia rebaudiana cultivated in Algeria for pharmaceutical purpose.

RESULTS: the main factor that enhance extraction yield has been isolated and was identified as the extraction temperature, among 3 temperatures the highest one (80°C) has shown the most effective extraction with an extraction yield of 19%. by using a purification method that combine the use of calcium hydroxide and ion exchange chromatography, we noticed a decrease in the total yield of extraction (4%) but with a product with a higher purity in rebaudioside A. to increase the purity of the isolated rebaudioside A, solvent cristallisation was performed using ethanol allowing to obtain rebaudioside A cristals. the obtained products after extraction, ,purification and cristallisation were characterized using microscopy, thin layer chromatography and infrared spectroscopy, the results of both analyses compared to the reference products results have shown the sucess of the extraction of rebaudioside A.

CONCLUSIONS: this study has allowed to optimize the extraction of rebaudiosides by understanding the factors influencing the process. The product obtained and characterized after purification and cristallisation was Rebaudioside A the most powerful sweetener present in Stevia, this product could be presented as a good excipient for the preparation of liquid and suspension formulations for diabetic patients.

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P1H-8

Effects of *Prunus spinosa L.* fruits on experimental wound healing

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BACKGROUND: A variety of medications and traditional approaches are used to improve the process of wound healing. *Prunus Spinosa L* (Rosaceae) is a therapeutic plant known since the ancient times. Extracts from the flowers have been used as diuretic, anti-inflammatory, spasmolitic and ''blood cleansing'' agents (1).

AIMS: We investigated the wound healing efficacy of the *Prunus Spinosa L.* using an excisional cutaneous wound model in mice. For this purpose methanol extracts of fruits prepared.

RESULTS: We used 32 number C57/Black mice in total; equally divided into four groups. The first group was set to be the control group to which we applied sunflower oil (Sunflower oil is known by its characteristic of being ineffective to the wound healing (reference molecule)). The second group was the vehicle group to which we applied glycerin and the third group was the *Prunus spinosa L* (Medicine) group. Lastly, the fourth group was named "Madecassol Group" to which we applied

a medical cream called Madecassol. The molecules were applied on the excisional wounds made on the back of the mice in all groups and the wound tissues were duly photographed. Through the inspection of the photographs taken, wound healing rates were calculated in digital measurement programs. Later, the wounded areas were cut out for fixation, and the tissues were embedded in paraffin. Hematoxylin-eosin (HE) and immunohistochemical (collagen type I, TGF β) staining and scoring were performed on five μm thickness sections taken from the tissues. Tissue sections were evaluated for histopathology. Wound healing was scored based on epidermal regeneration, granulation tissue thickness and angiogenesis (2). Less epidermal and dermal regeneration, medium-dense granular tissue, four to five veins in each section were observed in the control and vehicle group. For Madecassol and Medicine Group, we observed complete epidermal and dermal regeneration, dense granular tissue and more than seven veins in each section. In the immunohistochemical scoring, a few staining was observed in some of collagen 1, TGF β preparations of the control and vehicle groups. In those groups there were also some preparations which showed no staining. In the Medicine group, we observed statistically significant increase in staining similar to our observations in Madecassol Group.

CONCLUSIONS: Our findings support the beneficial effects of *Prunus Spinosa L.* for augmenting wound healing. The anti-inflammatory activities of *Prunus Spinosa L.* increased collagen synthesis whereas the number of inflammatory cells during wound healing was reduced and *Prunus Spinosa L.* may be beneficial for treating skin wounds.

Keywords: Wound, healing, *Prunus Spinosa L.*

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POSTER SECTION 2A
NOVEL DELIVERY SYSTEMS 2

P2A-1

Investigation of lidocaine base liposomes for transdermal delivery

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BACKGROUND: Nowadays there is an increasing interest in new, nanostructured delivery systems for local anesthetics, especially for dermal application because of its painless and easy application without the risk of systemic side effects. Liposomes are safe and effective drug carriers for topical delivery of drugs offering several advantages like biocompatibility, low toxicity, penetration enhancement of active ingredients and localization of the drug at the site of action.

AIMS: The aim of this work was to formulate and evaluate liposome formulations containing 0-10% w/w lidocaine. Large multilamellar vesicles composed of 1,2-dimyristoyl-sn-glycero-3-phosphocholine were prepared with the dry film hydration method and investigated in terms of particle size, polydispersity index, zeta potential, encapsulation efficiency and thermotropic behavior.

RESULTS: Particle size of the liposomes were in the range of 1844± 562.9 nm and 4842± 275.57 nm, growing with increasing drug concentration. Polydispersity index represented heterogenous populations (0.279± 0.25 to 1.000± 0.00). Zeta-potential value was barely influenced by the presence of the drug and altered around 0 mV. The determination of encapsulation efficiency with ultracentrifugation method, measuring the lidocaine content of the resuspended pellet, resulted 3.5-10.1 % encapsulation efficiency. DSC measurements confirmed the presence of lidocaine in the lipid bilayer of liposomes, as the main transition temperature of the liposomes shifted to lower temperature with the increasing drug concentration.

CONCLUSIONS: We successfully developed and characterized a liposome encapsulated lidocaine system, which could be a promising formulation for topical administration, however, further investigations are needed the evaluate the efficiency of the product.

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P2A-2

Characterization of prednisolone containing eye drop formulations by mucoadhesive – preservative system and cyclodextrin inclusion complex formation

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BACKGROUND: Topical administration of eye drops is restricted by the reflex mechanisms and complex structure of the eye. In the treatment of several ocular inflammations the applied, corticosteroid containing products are suspension formulations, which have low bioavailability therefore more frequent application is needed [1]. To reach the microbiological stability, the most commonly used preservative is benzalkonium-chloride, which cornea-cell apoptosis and irritation inducing effects are known [2]. These unfavorable attributes result the decrease of the patient-compliance. Considering these facts, development of eye drop formulations with increased efficiency and antimicrobial stability is necessary in the ocular therapy.

AIMS: Our aim was to develop and investigate a water-soluble prednisolone containing ophthalmic product by cyclodextrin inclusion complex formation, and mucoadhesive, preservative zinc-hyaluronate.

RESULTS: To solubilize the prednisolone the range of optimal cyclodextrin concentration was determined by phase-solubility test. The formulations contained the prednisolone in water-soluble condition. The concentrations of cyclodextrins were set which induce increased in vitro penetration of drug through semi-permeable membrane. The measured viscosity and surface tension were on the acceptable level. All formulations have mucoadhesive properties, significantly higher adhesive force was measured by tensile-test at the zinc-hyaluronate containing products. The microbiological stability of zinc-hyaluronate containing eye drops was sufficient according to the requirements of European Pharmacopoeia.

CONCLUSIONS: Water-soluble prednisolone containing, mucoadhesive, properly preserved eye drops were formulated with increased in vitro penetration. These innovative products could be appropriate in the treatment of inflammatory diseases of eye.

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P2A-3

Printing and characterization of antiviral and anticancer drug loaded film formulation by using inkjet printer

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BACKGROUND: Research in the field of personalized medicine has been increasing every year. There is a need for new drugs developed with personalized medicine approach for the treatment of diseases such as cancer with high intrasubject variability. Inkjet printing technique is promising for the development of personalized drugs with appropriate dose and pattern [1].

AIMS: The aim of this study was to prepare and characterize anticancer and antiviral drugs printed film formulation for the treatment of cervical cancer. Two different water-based ink formulations containing anticancer or antiviral drug were developed and printed on hydroxypropyl cellulose film with appropriate dose and pattern.

RESULTS: Different water-based ink formulations containing anticancer-cyclodextrin complex or antiviral drug bound to nanoparticles were successfully developed and printed on hydroxypropyl cellulose film with appropriate dose and pattern. Drug amount and release profile of film formulations were determined. Complete release of the anticancer drugs was reached within a period of 8h and the antiviral drug was reached within 16h. Mechanical properties and in vitro cell culture studies were performed for determination of the safety, efficacy and stability of films

CONCLUSIONS: This study showed that inkjet printing technique is favorable for the development of antiviral or anticancer drug-loaded personalized film formulations. Developed film seem to be a potential drug delivery system and good candidate for the treatment of cervical cancer. (Acknowledgement: Financial support by TUBITAK

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P2A-4

Formulation and study of fluoxetine containing mucoadhesive films

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BACKGROUND: Considering that orally administrated fluoxetine hydrochloride is mainly metabolised by the liver, its bioavailability may be improved by embedding into muco-bioadhesive pharmaceutical forms.

AIMS: The main objective of this work was the formulation of buccal mucoadhesive film containing fluoxetine hydrochloride, using different polymers in 5% concentrations. The effect of polymer type on the properties of films was also studied.

RESULTS: Three films were formulated: the first one containing only sodium-alginate, the second sodium-alginate and carboxymethylcellulose sodium and the third one sodium-alginate, carboxymethylcellulose sodium and Carbopol 940. Each film contained 100 mg fluoxetine. The film were prepared by solvent casting method. The diameters and weight was measured. Polymer type does not influence the diameter, but influences weight. Films containing only sodium-alginate possess the lowest weight, followed by those with combination two polymers. Results of drug content indicate homogenous dispersion of fluoxetine in the films, but concentrations vary depending on the polymer type. Highest values of swelling index and adhesive force were shown by films containing all three polymers. Dissolution curves demonstrate above 90 % of liberated fluoxetine in all cases, although differences may be observed among formulations.

CONCLUSIONS: Films containing three polymers present proper physical properties and after 5 minutes the dissolved amount of fluoxetine is 73%. In conclusion mucoadhesive films with fluoxetine hydrochloride containing sodium-alginate, carboxymethylcellulose sodium and Carbopol 940 may be used in clinical trials in order to develop a new pharmaceutical forms for the treatment of depression.

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P2A-5

Cross-linked chitosan microspheres for sustained nasal delivery of doxylamine and pyridoxine

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BACKGROUND: Spray-dried chitosan microspheres loaded with the drug combination of doxylamine succinate (DOX) and pyridoxine hydrochloride (PYR), intended for nasal delivery, were formulated in our previous study (1). The *in vitro* release of both drugs was fast, accompanied by an intensive burst effect, which imposed further optimizations of the particles release characteristics.

AIMS: The aim of the current study was to modify the polymer carrier by cross-linking the chitosan structure with glutaraldehyde before spray-drying in order to obtain microspheres with prolonged release of DOX and PYR.

RESULTS: Three cross-linked drug-loaded models were formulated via spray-drying using different concentrations of glutaraldehyde (0.01, 0.05 and 0.10 % *w*/*v*). The obtained microparticles were spherical in shape, with appropriate for nasal administration size (median diameter: 4.03 – 4.10 μm) and high drug entrapment efficiency (DEE: 82.24 – 93.14%). Only a slight decrease of the particle size and DEE was observed after the polymer cross-linking. With increasing the amount of the cross-linking agent both the swelling capacity of the carrier and the drug release rate were decreased. The cross-linked particles showed substantially reduced initial burst effect and prolonged release of DOX and PYR within 5h.

CONCLUSIONS: The cross-linking agent glutaraldehyde has a great influence on the swelling and drug release behavior of the spray-dried chitosan microspheres. The formulated cross-linked particles offer sustained release of the drug combination doxylamine/pyridoxine and could therefore be a promising drug delivery system.

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P2A-6

Microencapsulation of lavender essential oil via spray drying technique using chitosan and acacia gum as wall materials

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BACKGROUND: Lavender oil is an essential oil that has been widely used in food and aromatherapy. It has a variety of cosmetic applications as well as therapeutic purposes in herbal medicine. Emulsification and further microencapsulation of lavender oil is a reliable approach for the enhancement of its stability in terms of oxidation, chemical interactions, or volatilization. The determination of the hydrophilic-lipophilic balance (HLB) value of lavender oil appears as a crucial step for the development of stable emulsions, which is a prerequisite for the efficient oil encapsulation.

AIMS: Evaluation of optimum HLB value for lavender oil was the primary aim of the present study. Furthermore, optimization of spray drying parameters for lavender oil encapsulation in different encapsulating agents was pursued.

RESULTS: A series of emulsions with varied HLB values (8÷12) were developed and the stability of the formulated coarse disperse systems was evaluated in terms of droplet size distribution, degree of creaming, effect of centrifugation and turbidimetry. According to the results, HLB=10 was selected as optimum for the development of emulsions of satisfactory thermodynamic stability. The formulated emulsions were further spray dried and the obtained powders were characterized in terms of particle size distribution and oil encapsulation efficiency. The influence of wall material type and concentration, as well as polymer/lavender oil ratio were evaluated.

CONCLUSIONS: The assessed characteristics of the microcapsules were slightly influenced by the polymer/oil ratio. A major trend towards increased encapsulation efficiency was noted when higher polymer concentrations were used. Both wall materials appeared to be relevant for microencapsulation of lavender essential oil.

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P2A-7

Biotin and glutathione targeting of solid nanoparticles to cross human brain endothelial cells

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BACKGROUND: Pharmaceutical treatment of disease of the central nervous system is far from satisfactory due to the poor penetration of therapeutic drugs to the brain (1). Ligands of endogenous transporters of the blood-brain barrier (BBB), the major obstacle to prevent potential neuropharmaceuticals, can be used as targeting vectors for brain delivery of drugs encapsulated in nanoparticles (2).

AIMS: We tested biotin-labeled solid nanoparticles for the first time and compared to glutathione-labeled nanoparticles in brain endothelial cells.

RESULTS: Neutravidin coated fluorescent polystyrene nanoparticles were derivatized with biotin and biotinylated glutathione. Cell viability by MTT-test, uptake and transfer of the nanoparticles across hCMEC/D3 human brain endothelial monolayers were measured. The uptake of the nanoparticles was visualized by confocal microscopy. The tested nanoparticles caused no change in cell viability. The uptake of biotin- and glutathione-labeled nanoparticles by brain endothelial cells was time-dependent and significantly higher compared to non-labeled nanoparticles. The uptake was verified by microscopy, targeted nanoparticles could be demonstrated in hCMEC/D3 cells.The penetration of the glutathione-labeled nanoparticles across the endothelial monolayer was higher than the biotin-targeted ones.

CONCLUSIONS: : Biotin as a ligand increased the uptake and the transfer of nanoparticles across brain endothelial cells. Glutathione was more effective as a ligand to increase nanoparticle permeability through endothelial monolayers supporting its use as a brain targeting vector.

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P2A-8

Targeted delivery of vesicular nanoparticles across a culture model of the blood-brain barrier

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BACKGROUND: Efficient drug delivery across central nervous system (CNS) barriers is a central problem in pharmaceutical treatment of neurological diseases (1). Most pharmaceutical drug candidates including hydrophilic molecules, biopharmaceuticals, and efflux transporter ligands have a low permeability across the blood-brain barrier. Targeted nanoparticles are new tools to increase drug delivery to brain (2).

AIMS: The aim of our study was to compare different ligands of transporters present at the blood-brain barrier for targeting vesicular nanoparticles.

RESULTS: Non-ionic surfactant and cholesterol based nanoparticles, so-called niosomes were derivatized with glucopyranose, alanin and glutathionen using lipid or PEG linkers. The cargo of the niosomes was Evans blue-albumin complex. Treatments with niosomes did not influence the viability of primary rat brain endothelial cells. The presence of targeting ligands on niosomes increased the uptake of the cargo molecule in cultured brain endothelial cells. The cellular uptake of niosomes was temperature dependent and could be decreased with a metabolic inhibitor indicating an active transport process. Targeting ligands elevated the permeability of the cargo across brain endothelial monolayers.Treatment with niosomes increased plasma membrane fluidity in endothelial cells, suggesting the fusion of the nanovesicles with the cell membranes.

CONCLUSIONS: Our data indicate that nutrient transporter ligands can potentially be exploited for CNS targeting of nanoparticles.

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P2A-9

Dexpanthenol/PCL nanofibers for wound healing: Preparation and in-vitro characterization

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BACKGROUND: Dexpanthenol (DEX) has been widely used to treat mucous membrane lesions and skin wounds in traditional formulations (1). The nanofiber mat covers the wounded area, protects the damaged skin and stimulates wound healing process by active agents (2).

AIMS: In this work, DEX loaded PCL nanofiber mats was prepared for the first time. The formulations were characterized by microscopic observations, measurement of thickness of nanofiber mats. FT-IR analyses of formualtions were performed. Mechanical properties, swelling ability, loading capacity were investigated. In-vitro release behavior was studied with dialysis bags.

RESULTS: In this work, DEX loaded PCL nanofiber mats was prepared for the first time. The formulations were characterized by microscopic observations, measurement of thickness of nanofiber mats. FT-IR analyses of formualtions were performed. Mechanical properties, swelling ability, loading capacity were investigated. In-vitro release behavior was studied with dialysis bags.

CONCLUSIONS: DEX loaded PCL nanofiber formulation was prepared successfully with suitable properties for topical application.

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P2A-10

Development of inkjet printed levothyroxine formulations - towards personalized dosing

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BACKGROUND: The advantages of digital printing are well translated to the emerging trend of

personalized medicine in the pharmaceutical field. Inkjet printing technology has shown to allow rapid, accurate and flexible deposition of drug containing ink onto edible substrates. However, in depth understanding about formulation development and production is still needed.

AIM: The purpose of the study was to develop an ink formulation with levothyroxine (T4) and to print escalating doses onto a bilayered edible substrate. Furthermore, dose repeatability of two parallel batches and the stability of the printed formulations were evaluated at long-term (25°C, RH 60%) and accelerated (40°C, RH 75%) storage conditions.

RESULTS: Stable drop formation, a prerequisite for dose uniformity, was demonstrated for the T4 (20 mg/ml) ink formulation having DMSO and propylene glycol (PG) as solvents. Therapeutic doses of T4 (40-590 μg) were prepared by printing two dose escalation sets with resolutions of 200 and 400 dpi. The doses were quantified by HPLC. Dose repeatability was studied for the 400 dpi samples and RSD of <4.1% was calculated for the parallel batches. Drug degradation was evident for the T4 doses after 6 weeks. The ink component PG contributed to prolonged drying times and therefore degradation of the drug.

CONCLUSIONS: Therapeutically relevant doses were printed. Remarkable drug degradation was observed between doses stored at different storage conditions. The viscosity increasing agent, PG, contributed to prolonged drying. It would appear that the PG-% should be decreased or replaced in the ink formulation and more efficient drying should be implemented to improve the stability of the printed drug delivery systems.

P2A-11

Brinzolamide microemulsions as alternative carriers against glaucoma disease

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BACKGROUND: Glaucoma, is the second leading cause of the optic nerve damage and vision loss, internationally [1]. The main therapeutic agents of glaucoma are b-adrenergic blockers such as atenolol, butanolol etc as well as carbonic anhydrase inhibitors. Brinzolamide, a carbonic anhydrase inhibitor lowers the intraocular pressure found in glaucoma but its low solubility limited its pharmacological action. In addition to this, the fact that ocular concentional drug delivery systems results in poor bioavailability given the lacrimal secretion and nasolacrimal drainage of the eye leads the researchers to design novel ocular carriers such as microemulsions [2].

AIMS: The aim of this work was the preparation of novel oil-in-water micromemulsions containing three different concentrations of Brinzolamide (0,2, 0,5, 1% w/v). Pseudo-ternary phase diagrams were constructed for combination of isopropyl myristate as oil phase, Tween 80, Cremophor EL and Span 20 as surfactants, ethanol as co-surfactant and distilled water as aqueous phase. The drug was added to the oil phase and mixed vigorously. The properties of microemulsions, such as stability, FT-IR spectrum, pH in the absence or presence of Brinzolamide were evaluated. In vitro release studies were performed using simulated organic tears and the release time was 24 h.

RESULTS: In vitro release exhibited different release patterns which differentiated by the concentration of the drug as well as excipients presence. FT-IR spectroscopy studies showed that the microemulsions present some possible interactions which induced the enhanced release of brinzolamide. In further, pH values of the prepared microemulsions ranged between 6.2-7 which are acceptable. Stability studies in terms of clarity and separation were found promising.

CONCLUSIONS: In conclusion, Brinzolamide microemulsions were succcessfully developed and found to be an alternative option for glaucoma treatment.

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P2A-12

Development of alginate microspheres containing essential oils microemulsions: Laser diffractometry characterization and loading capacity optimization by response surface methodology.

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BACKGROUND: Due to the their multitude bioactivities, the formulation of plant biomolecules, such as plant extracts and essential oils (EO), has been highly studied for a lot off applications, from food flavor industry to phytopharmaceutical and cosmeceutical applications; In aims of drug release control as response to several inductions, and also to bioactivities enhancing, Ionic Gelation (IG), a chemical method, highly recommended for the encapsumlation of hydrophobic bioactive agents such as EO.

AIMS: To obtain small particles size allowing high drug loading capacity, the studied EO was, firstly formulated on microemulsion, then, secondly microencapsulated using biodegradable polymer; The Response Surface Methodology was applied to investigate fourth experimental parameters (polymer concentration, cross-linking agent concentration, mixing time and mixing velocity), considering multiple responses which are the loading capacity of the obtained microsphers and their related surface/volume parameters.

RESULTS: The physical characteristics of the microspheres were assessed by laser diffractometry (Mastersizer 2000 Ver. 5.60, Malvern Instruments Ltd) and calculated on the basis of surface/ volume related parameters: Specific Surface Area, *D[3,2]* and *D[4,3]*. Also, Scattering Electronic Microscopy (SEM) observations were used to visualize the manner that the essential oil is microencapsulated.

The selected optimal conditions allow to microparticles with Specific Surface Area from 0.011 to 10,1 m^2/g; a mean Surface Weight with a range of 0.595 to 547.735 μm and a mean Volume Weight from 5.392 to 714.263 μm. The loading capacity of 4,95 to 15,19% was allowed. The SEM observations showed that the studied EO was loaded according to the matrix solution system.

CONCLUSIONS: In conclusion, it is demonstrated that EO microemulsions can be microencapsulated under alginate microspheres with acceptable particles size characteristics and an interesting loading capacity for these volatile natural products.

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P2A-13

Assessment of etofenamate loaded microemulsion formulations for transdermal drug delivery: preparation, characterization, stability and in vitro release

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BACKGROUND: Transdermal drug delivery system was designed to sustain the release and improve the bioavailability of drug and patient compliance. Microemulsions are colloidal dispersions which have features to be chosen such as being thermodynamically stable, consist of oil, aqueous, surfactant and co-surfactant. The active substance, Etofenamate (ETF), works as analgesic, antirheumatic, antipyretic and anti-inflammatory (1,2).

AIMS: This study aimed to obtain and characterize microemulsion containing ETF for transdermal delivery. Microemulsions were prepared by titration method. The ETF was incorporated in the proportion of 5% in microemulsions containing oleic acid as oil, Cremophor EL, Span 80, Tween 20 as surfactants, ethanol and Transcutol HP as co-surfactant and distilled water as aqueous. All the formulations were subjected to droplet size, polydispersity index (PDI), zeta potential, ETF amount, pH and conductivity measurements and stability studies. Also, *in vitro* drug release was evaluated using Franz diffusion cells.

RESULTS: Four different ETF loaded microemulsions were developed successfully using phase diagrams. All formulations had appropriate observed pH values for dermal application. ETF loaded microemulsions exhibited low droplet size and PDI. Microemulsions were not electrically charged (zeta potential equal to 0 mV) due to their ionic characteristics. Regarding physicochemical values, no significant changes in the values measured at the beginning of the study were obtained after the stability period. The obtained *in vitro* release results of microemulsions showed a slow release behavior. The cumulative drug release rate of M4 within 24 h was higher than other microemulsions.

CONCLUSIONS: Consequently, these MEs result in a promising alternative for further *in vivo* evaluation. This study illustrated that ETF-microemulsions have a good potential for dermal application.

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POSTER SECTION 2B NANOPHARMACEUTICALS 2

P2B-1

Development and evaluation of nanocomposite-based "nanoantibiotics" in vitro and in vivo

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BACKGROUND: Antibacterial nanoparticles are known to control infectious diseases in a more effective way by providing enhanced pharmacokinetics of drugs such as site-targeted delivery, controlledrelease and better solubility, and also accumulate to provide effective therapeutic effects, in contrast to the conventional antibiotics [1].

AIMS: This study focuses on the development and investigation of the antibacterial activity "nanoantibiotics", composed of inorganic & organic constructs..

RESULTS: The proposed nanocomposite-based nanoantibiotics were successfully prepared with in the range of 400 nm ,approved by TEM images. The success of nanoantibiotics design was proven in each step of preparation by zeta potential measurements of the suspension of the prepared particles. The cytocompability of nanoantibiotics were determined by using CaCo-2 cell line as in vitro cell model with the WST-1 assay. In vitro bacterial growth inhibition results showed significant inhibition by the improved design of antibiotics from inorganic core to inorganic & organic nanocomposites. Ruptured bacterial cell membranes was observed when the bacteria were treated with the nanobiotics by TEM imagings The efficient localization of the nanobiotics in the intestines of D.melanogaster was visualized through wide-field fluorescence imaging after feeding the flies with nanoparticle homogenized fly food.

CONCLUSIONS: The observed growth inhibition results from the in vitro experiments revealed that multiple antibacterial constructs in the designed nanobiotics system helps to improve its antibacterial activity. The operability of the nanobiotics in the in vivo animal model has been assured.

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P2B-2

Sertaconazole loaded nanofibers as topical drug carriers

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BACKGROUND: Electrospun nanofiber mats offer several desirable features as topical drug delivery systems. The high surface area to volume ratio of fiber mats provide efficient delivery of both hydrophilic and hydrophobic drugs and, drug release can be modulated by functionalization of the nanofibers (1).

AIMS: The purpose of this study was to formulate sertaconazole (a highly lipophilic antifungal drug) loaded polymeric nanofibers by the electrospinning technique for topical administration. The morphology and size of polyurethane based nanofibers were visualized by scanning electron microscopy (SEM) and drug-excipient interaction was studied by ATR-FTIR spectroscopy. In vitro skin penetration of sertaconazole from optimized nanofibers was examined with tape stripping technique.

RESULTS: The electrospinnig process produced nanofibrous mats with uniform structure and with narrow size distribution. ATR-FTIR spectroscopy indicated interaction between the the drug and the polymer. In vitro skin penetration study revealed effective sertaconazole accumulation in the pig skin from the polymeric nanofibers.

CONCLUSIONS: In conclusion, sertaconazole loaded homogeneous composite nanofibrous mats could be potential candidates in topical antifungal drug delivery.

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P2B-3

Synthesis and characterization of apigenin loaded novel HSA/galactomannan/chitosan nanoparticles for pulmonary drug delivery

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BACKGROUND: Pulmonary delivery of a pharmacologically active ingredient offers numerous advantages over other administration routes due to the large surface area, high permeability and low enzymatic activity of the lungs. Inhalable formulations consisting of nanoparticles (NPs) are gaining interest in terms of controlling drug release and improving deposition. Serum albumin NPs are effective tools for delivering poorly water soluble phytoconstituents[1]. Apigenin (Api), a poorly water soluble flavonoid, has remarkable health effects such as antioxidant, anti-inflammatory and anticancer properties and was classified as Biopharmaceutical Classification System (BCS) II. drug[2].

AIMS: The aim of this work was to synthetize and characterize novel biocompatible HSA/galactomannan/chitosan NPs, loaded with a poorly water soluble Api.

RESULTS: The HSA-galactomannan conjugates were prepared by Maillard reaction at 60°C and 80% relative humidity. As the next step, the chitosan solution was added and stirred for 1 hour to obtain HSA/galactomannan/chitosan NPs. The physical properties of the NPs such as particles size, zeta potential and viscosity as well as drug loading efficiency were measured. The samples were further lyophilized and dissolution of Api was determined with Franz cell apparatus. The residual water content was investigated by Karl-Fischer titration.

CONCLUSIONS: Our results indicate that the NPs have adequate size and apigenin could be effectively loaded into the nanoparticles with enhanced dissolution.

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P2B-4

Development of a nasal powder preformulation process by Design of Experiment method

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BACKGROUND: The nasal delivery of drugs offers a great alternative route to to increase patient compliance due to its advantageous properties. Nasal powders have better adhesion due to the additive polymers that may be e.g. gelling or good wettability agents, thus the bioavailability of powders is better compared to the liquid formulations. Using nanoparticles, innovative products can be achieved, which may lead to the improvement of different therapies. Co-milling is an economically and environmentally desirable method to produce nanoparticles. Lamotrigine (LAM) was used as a model drug and polyvinyl- alcohol (PVA) was chosen to provide a polymer matrix for the nanoparticles.

AIMS: The aim of our study was to determine the optimal parameters of co-milling using Design of Experiment (DoE) as a part of Quality by Design. By DoE it is possible to estimate the proper operating conditions of co-milling, which is called Design Space. Another goal is to investigate the prepared products that includes physico-chemical (XRPD, DSC, polarity, solubility), *in vitro* dissolution and Side-bi-Side horizontal diffusion tests.

RESULTS: The dependent variables of DoE based factorial design are LAM:PVA ratio, milling time and speed, the independent variables are particle size and dissolution rate. The particle size determination shows that the size of LAM in the products is between 142 nm and 2.42 μm. The *in vitro* dissolution of LAM from the samples is between 43.38 and 100%. However, the Design Space of milling will be set up in the near future, and then the optimal parameters will be determined.

CONCLUSIONS: The results of particle size measurement and dissolution investigations show a promising preparation method to produce powders that contain nanonized LAM for nasal application.

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P2B-5

Comparison study of nanonized meloxicam and its potassium salt containing peroral dosage form with fast release

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BACKGROUND: According to the guidelines developed by the World Health Organization, NSAIDs (non-steroidal anti-inflammatory drugs) are used as initial treatment in both malignant and non-malignant pain therapy [1]. The solubility of NSAIDs is pH dependent (low solubility in acidic medium), and their permeability is relatively high ($logP_{app}$ 1-3). Therefore their particle size reduction or salt form can increase the dissolution rate/solubility to reach a fast analgesic effect [2].

AIMS: Our aims were to produce nanonized meloxicam (MEL) as NSAID to achieve faster dissolution in order to prepare solid dosage form for peroral administration; moreover, to compare the dissolution characteristics with its potassium monohydrate (MELP) at pH 1.2.

RESULTS: Combined wet milling technology resulted in nanonized MEL (≈136 nm): stable in nanosuspension form. MEL containing nanosuspension was applied to develop solid drug delivery systems (DDSs). For comparison study, MELP containing DDS as an interactive physical mixture was used. It was found that the equilibrium solubilities of MEL and MELP are the same; nonetheless, the difference in their rates and extents of dissolution is considerable.

CONCLUSIONS: Our comparison study led to a new approach of developing MEL and MELP containing DDSs with fast release for pain therapy.

The work was supported by Foundation for Development of Pharmacy Education at University of Szeged

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P2B-6

Formulation and in vitro characterization of inhalable nano-structured dry powders

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BACKGROUND: The formulation of inhalable dry powders aggregated of nanoparticles is gaining much attention in the pharmaceutical research area. The appropriate particle engineering technique is the most important factor to get enhanced aerosolization properties and an improved therapeutic effect. Not only the preparation method, but the exact aerodynamical characterization, too, gives important feedback for the further formulation methods.

AIMS: Our aim was to produce inhalable nanostructured powders, containing non-water-soluble active pharmaceutical ingredients (ACI), with a two-step wet mill (Bartos Cs., 2016) and co-spray drying technology (Chvatal A., 2017). We also aimed to characterize the efficacy of the prepared samples with in vitro aerodynamical characterization (Andersen Cascade Impactor).

RESULTS: We used a two-step inhalable nanoparticle preparation. First, the nanoparticle-size pre-suspension was prepared with wet milling technology. The final micro-sized powders were obtained with the co-spray drying of the diluted suspension and aerosolization enhancer excipients (L-leucine, ammonium carbonate). The electron microscopy pictures showed spherical particles, while the in vitro aerodynamic characterization gives an exact profile of the powder dynamics.

CONCLUSIONS: We successfully worked out a nanoparticle preparation method by combining the wet milling and spray drying methods, with the use of which we could achieve the enhanced deposition of the samples.

This project was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences (2014–2017).

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P2B-7

Application of dry milling technique in order to prepare intranasal powder with nanonized levodopa

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BACKGROUND: Levodopa is the most commonly used medication in treating Parkinson's disease. However, the delivery of oral levodopa is associated with adverse effects. Intranasal administration is an alternative route for the delivery of levodopa to reach the systemic circulation due to the transepithelial absorption or directly the brain tissues through the axonal pathway (1).

AIMS: In the present work, the use of dry milling in order to increase the bioavailability of levodopa, marked out for intranasal crisis therapy as dry powder, is reported. The aims of our work were to reduce the particle size of the drug to the nanometer range by using a planetary ball mill, with the optimization of the process parameters (milling time, speed of revolution) and excipients, and to study the effects of milling on the physicochemical properties and *in vitro* diffusion of levodopa.

RESULTS: During milling, sodium hyaluronate and chitosan were used as additives. Various drug-carrier ratios were treated. The average particle size of the products, detected by laser diffraction, was reduced to the micrometer range in the presence of chitosan. The particle size of levodopa was obtained by analyzing several scanning electron microscopy (SEM) images with the ImageJ software environment. It can be concluded that the size and morphology of the drug (~50-100 nm/ roundish) have changed due to milling. The determination of the structure of levodopa by differential scanning calorimetry and X-ray powder diffraction revealed the amorphization of the drug after milling (50-80% of the drug remained crystalline). *In vitro* permeability studies were carried out on a modified horizontal Side-Bi-Side™ cell model, simulating the conditions of the nasal cavity.

CONCLUSIONS: The high specific surface area and rapid dissolution of levodopa nanoparticles resulted in the high permeability of the drug in case of milled products.

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P2B-8

Effects of different stability conditions on three-layered doxycycline collagen loaded nanofiber wound dressing

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BACKGROUND: Electrospinning is the most used method to produce nanofibers (1). Nanofiber wound dressing have unique properties, such as high porosity and surface area. Nanofibers can undergo different changes that will influence their structure and performance. Therefore, it is necessary to determine the stability properties of the dressing in different conditions.

AIMS: The aim of this study is to determine physicochemical properties of nanofiber wound dressing at three different conditions according to ICH guidelines (4°C/ambient humidity, 25°C/60% RH and 40°C/75% RH) for 12 months. At appropriate time intervals, some characterization parameters such as drug content, tensile strength and work of bioadhesion value were determined and SEM images of the nanofibers were obtained.

RESULTS: Temperature and relative humidity affect the fiber structure negatively both at 25°C/60% RH and 40°C/75% RH conditions due to moisture. The nanofiber structure was completely deteriorated and the light yellow colored wound dressings turned to brown. For this reason, stability studies were completed at only 4°C/ambient humidity conditions for 12 months. It was observed that there were no significant changes in the stability test parameters that could negatively affect the use of wound dressing ($p>0,05$).

CONCLUSIONS: As a result of the stability studies, it was found that the morphological, mechanical, bioadhesion and wettability properties and the amount of doxycycline remained stable for a period of 12 months at 4°C/ambient humidity condition. It is appropriate to carry out the stability studies with different packaging material so that the nanofiber wound dressing can be stored at higher temperature and humiditiy condition.

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P2B-9

Freeze-drying of Bovine Serum Albumin as potential nano drug delivery system

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BACKGROUND: Bovine Serum Albumin (BSA) is playing an increasing role as a Drug Delivery System (DDS) in the clinical therapy. Due to its biocompatibility and non-toxicity, it can be used as a pharmaceutical carrier more safely versus many synthetic polymers. BSA is also an excellent material to construct nanoparticles because it has good physicochemical stability, targetability, and chemical functionality. Freeze drying is a suitable technique to improve the long-term storage stability of colloidal DDSs such as nanoparticles.

AIMS: Our aim was to apply the freeze drying technology, as commonly used method for protein stabilization to prepare nano DDS from BSA as model protein. Further aim was to characterize the physicochemical changes of the BSA and investigate the effect of additives.

RESULTS: BSA based nano DDS was prepared using different concentrations of phosphate buffered saline (PBS), by means of coacervation method resulting in nano range preparation. After purification of nano particles, freeze-drying was carried out with trehalose as cryoprotectant. Consistent with Fourier-transform infrared spectroscopy (FTIR) data trehalose partially prevented structural perturbations in BSA upon freeze-drying. Thermal analysis (TA) and X-ray powder diffraction (XRPD) were used as physicochemical characterization methods. The desired particle size (130 nm) and zeta potential (-31,8 mV) was reached by optimization of the composition.

CONCLUSIONS: BSA based nano DDS can be prepared by means of coacervation and freeze-drying with desired properties (size, zeta potential, stability). The formulated BSA based nano DDS can be applied for drug conjugation and –delivery.

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POSTER SECTION 2C
QUALITY BY DESIGN

P2C-1

Improving protein product quality through real-time bioprocess control based on Raman spectroscopy

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BACKGROUND: Raman spectroscopy is an optical spectroscopy technique that provides a molecular fingerprint of a sample and enables nondestructive analysis of chemical composition and molecular structure. Applications of Raman spectroscopy in polymer, pharmaceutical, bioprocessing, and biomedical analysis have strongly increased in the past three decades as laser sampling and detector technology has improved. Because of these technological advances, Raman spectroscopy is now well recognized as a practical analysis technique inside and outside the biopharmaceutical laboratory. The quality of therapeutic CHO cell culture proteins is a result of the entire production process. Producing therapeutic proteins with consistent characteristics is a challenging task which requires a high level of process understanding and maintaining process conditions within an optimal batch trajectory.

AIM: The goal of the case studies were to accelerate understanding of biopharmaceutical production processes and integrate a robust real-time process control strategy.

RESULTS: Case studies in the presentation will illustrate the impact of Raman based bioprocess control to the cells, the cell culture environment, the yield, and finally to the quality of therapeutic proteins [1]. Results of the case studies will provide valuable insights into effective control strategies and explicate the successful transfer of analytical Raman methods from process development to GMP manufacturing.

CONCLUSION: In situ Raman spectroscopy enables simultaneous monitoring of multiple product quality relevant parameter and allows for in-process corrections. Precise navigation and smart adaptation of critical upstream process conditions based on Raman spectroscopy reduces the complexity of producing high quality products.

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P2C-2

Initial Risk Assessment as part of the Quality by Design in peptide drug containing formulation development

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BACKGROUND: The Quality by Design (QbD) concept is a knowledge, risk based, holistic and proactive manner of pharmaceutical developments which results in a better product and process understanding. The key element of the QbD method is the Risk Assessment (RA). The whole QbD thinking and RA are even more important and essential in case of biological products due to their complexity and nature[1-2].

AIMS: The aim of this study is the risk assessment based planning and evaluation of an oral peptide delivery system; to develop a flow chart of necessary decision needed steps and also methodology for evaluating potential risk factors.

RESULTS: The outcome of this development is the collection and presentation of parameters which influence the quality, safety and efficacy of the aimed oral peptide containing product and its formulation process. The influencing factors (characteristics of raw materials, environmental and instrumental factors, formulation characteristics, carrier system's properties etc.) are presented by applying Ishikawa diagrams. The potential critical quality and process parameters are identified as next step and the initial RA process is presented. The outcome of RA is resulted in the ranking of the critical factors according to their effect and importance. Ranking results are visualized in Pareto-, and severity-occurrence charts, by means of the RA software (Lean QbD®).

CONCLUSIONS: Biological products, peptide containing drugs are special due to their bioactivity, immunogenicity, chemical diversity, safety aspects, etc. Their formulation is also more complex, therefore a more detailed planning, prior thinking and deep understanding of the risk factors will led to a proper product performance and quality. The key of this quality planning methodology is the QbD and RA based approach, which was found to be very useful in early phase developments in many cases[3-4] and it also can be offered in case of peptide containing formulations.

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P2C-3

In-line Raman spectroscopic monitoring and feedback control of a continuous pharmaceutical powder blending and tableting process

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BACKGROUND: Spreading of continuous pharmaceutical manufacturing is anticipated in the next decades [1]. However, the integration of Process Analytical Technology (PAT) initiative into continuous processes is indispensable for reliable continuous production.

AIMS: The aim of this study is to implement in-line Raman spectroscopic monitoring and feedback control in a continuous blending and tableting process, two fundamental unit operations in the production of multicomponent solid dosage forms. This is the first application of Raman-spectroscopy in continuous homogenization and the first ever Raman-based feedback control in the formulation technology of solid pharmaceuticals.

RESULTS: Continuous blending and tableting experiments were conducted using a two-component model system of caffeine and glucose. The real-time analysis of API content in a two-component blend, the blend homogeneity, and tablet content uniformity was performed using a Partial Least Squares (PLS) quantitative method. The in-line Raman spectroscopic monitoring showed that the applied twin-screw continuous blender was capable of producing blends with high homogeneity, uniform composition. Furthermore, technological malfunctions could be detected by the proposed PAT method. The Raman spectroscopy-based feedback control of the API feeder was also established, which guarantees the required API content during the continuous blending.

CONCLUSIONS: The Process Analitically Controlled Technology (PACT) approach presented in

this study proves the feasibility of Raman spectroscopy for monitoring and control continuous processes and could be extended to several manufacturing steps, therefore contributing to the development of fully continuous manufacturing, minimizing the possibility of out-of-specification products and the need for time-consuming off-line analysis.

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P2C-4

Quality by Design based approach in the development of dermatological dosage forms

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BACKGROUND: Dermal formulations receive more and more attention in the pharmaceutical and cosmetic fields. Due to the fast market growth, a larger emphasis has been placed on proper planning of the product development and on using modern tools such as the Quality by Design (QbD) concept [1]. In such a way the duration of the development process and its costs can be reduced, while being able to meet the requirements of the stakeholders, namely the patient, the industry and the regulatory authorities more precisely.

AIMS: The aim of our present work was to adapt ICH Q8 guideline on the Quality by Design based approach for the development of dermatological dosage forms.

RESULTS: The QbD concept involves identifying the quality target product profile (QTTP), the critical material attributes (CMAs) and critical process parameters (CPPs) into the critical quality attributes (CQAs) of a drug product at the beginning of the development [1]. The quality management tools (e.g. Ishikawa diagram, Pareto analysis, risk estimate matrix etc.) and the Design of Experiments (DoE) techniques within the risk assessment process are key elements of QbD methodology. LeanQbD Software and StatSoft. Inc. Statistica for Windows were applied to indentify the risks. The model system was a Nanostructured Lipid Carrier (NLC) preparation. The most critical CMAs and CPPs were chosen to be the independent variables and the CQAs were chosen to be the dependent variables in the 2^3 factorial design process. Based on our experiments, an optimal formulation can be obtained [2].

CONCLUSIONS: The information received was very important for the pharmaceutical development, on the basis of these results the control strategy can be designed and it ensures a safe and effective dermal product that meets the quality expectations of the relevant stakeholders.

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P2C-5

Preparation of orally dispersible tablets of ziprasidone hydrochloride monohydrate nanocrystals: The Quality by Design (QbD) approach

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BACKGROUND: Ziprasidone hydrochloride monohydrate (ZHM) is a poorly soluble active substance which is belong to BCS Class II drugs and used for schizophrenia treatment. Orally dispersible tablets (ODTs) are most common dosage forms for patient compliance and using QbD for development ODTs have advantages about establishing optimum composition. In this study ZHM nanocrystals were produced by high pressure homogenization using PVP K30[1] as stabilizer to solve solubility issues of ZHM. ODTs were prepared with ZHM nanocrystals and formulations were designed according to QbD to optimize tablet compositions in terms of disintegrating agent (Acdi-sol) and lubricant (Mg stearate) ratio. 3^2 full factorial design was performed and tablets were prepared by direct compression method. The effects of interactions on dependent variables (hardness, friability and disintegration time) were investigated. Design spaces were obtained and disintegrant and lubricant amount were determined.

AIMS: The aim of this study was to develop ZHM containing ODTs for treatment of schizophrenia and enhancing water solubility of ZHM to improve oral bioavailability by developing nanocrystals of ZHM.

RESULTS: Nanocrystals characterized with 400-600 nm particles size, 0.1-0.4 particle size distribution and >20 mV zeta potential values used to

prepare ODTs. Disintegration time was shorter in nanocrystal ODTs then physical mixture ODTs while similar results were observed in terms of friability and hardness. Friability, hardness and disintegration time values of nanocrystal ODTs were found 1.05%, 26.1 N and 6.0 seconds, respectively.

CONCLUSIONS: Nanocrystal ODT formulations were developed successfully. The results showed that this new formulation could be an alternative pharmaceutical form with improved water solubility.

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P2C-6

Raman spectroscopy based feedback control of the enzymatic hydrolysis of lactose

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BACKGROUND: Production of pharmaceuticals requires an efficient process control strategy to ensure product quality. The Process Analytical Technology (PAT) initiatives have triggered the development of real-time process monitoring and process control in the pharmaceutical industry. Raman spectrometry has special significance as an analytical tool for inline monitoring of pharmaceutical processes. With the aid of real-time multivariate data analysis, the quantitative information extracted from the spectra can be utilized in a control system. There's a great advantage in the use of Raman spectrometry in biotechnology for the monitoring and control of the production of biotechnology-derived medicines (e.g. monoclonal antibodies).

AIMS: In this work the enzymatic hydrolysis of lactose was chosen as a model bioprocess for developing closed-loop feedback control system based on inline Raman spectrometry. For this purpose a real-time data analyser programm and an effective control system was developed to maintain the lactose concentration.

RESULTS: Real-time Raman spectra evaluation was accomplished using classical least squares (CLS) and partial least squares (PLS) multivariate data analysis methods. After optimization of the lactose hydrolysis, the control of lactose concentration could be achieved with CLS method. To improve real-time evaluation, PLS method was used resulting in better evaluation of spectra. Comparing the two chemometric methods, the PLS method gave better results in the control experiment of lactose hydrolysis than CLS evaluation method.

CONCLUSIONS: Raman spectrometry based feedback control of the enzymatic hydrolysis of lactose shows the potential opportunities of Raman spectrometry in other bioprocesses where the control of the medium component concentration is important.

P2C-7

Defining of the design space and development of an in-line NIR monitoring method for the fluidised bed granulation process of two APIs

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BACKGROUND: The modern drug development and manufacturing is expected to be carried out following a quality by design (QbD) approach and applying in-line monitoring methods as process analytical technology (PAT).

AIMS: Applying an experimental design in order to optimise a fluid bed granulation process of 2 APIs simultaneously. Process optimisation through systematic evaluation of the influence of minor changes of the API / excipient sort or critical process parameters, on the process itself and the final product quality. Development of an in-line near infrared (NIR) method which would allow the water content monitoring along the process.

RESULTS: The developed D-optimal experimental design registered a G-efficiency of over 70 and a condition number of under 7.1, values which describe a good optimisation design. The design contained 2 critical process parameters as quantitative factors and different sorts of APIs and microcrystalline cellulose as qualitative factors. During the process, the relative humidity of the granules was between 1 and 19%. Those values were then used to calibrate the preprocessed NIR spectral data, developing an OPLS model with R2X greater then 0.9. The model allowed the in-line process control by predicting the water content throughout the process and the establishment

of the granulation end point. Applying the described experimental design, the design space could be specifically defined in accordance with all the possible changes of the API or excipient specifications, thereby providing an end product meeting the quality target product profile. Moreover, during the in-line process monitoring, the changes of critical process parameters were well underlined, allowing the identification of the granulation steps, facilitating the process control and ensuring a high reliability of the process.

CONCLUSIONS: The described, systematic approach provided a thorough understanding of the fluid bed granulation and its variables, allowing the development of a robust, fully controlled process.

P2C-8

Multivariate Data Analysis (MVDA) applied for the development, process understranding and real time monitoring of mannitol based granulates loaded with loratadine by solution layering

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BACKGROUND: The development of a pharmaceutical product relies on the identification and control of formulation and process variables that influence the product's critical quality attributes (CQAs). This objective can be fulfilled by applying Design of Experiments (DoE) and by implementing process monitoring instruments for real time quality testing as recommended by guidelines published for the industry.

AIMS: The objective of this work was to develop mannitol based granulates loaded with loratadine by applying multivariate data analysis for process understanding and in-line monitoring via NIR technology.

RESULTS: To identify most relevant formulation and process variables five factors (atomizing pressure, pulverization rate, %Water, %PVP, raw material particle size distribution) were screened through a Fractional Factorial Design with resolution V. Mean particle size was influenced by atomizing pressure, pulverization rate and water content of the pulverized solution. Differences in granule flowing properties could be attributed mainly to atomizing pressure, water content and raw material particle size distribution. The PVP concentration mainly influenced disintegration and the size of the 0-300 μm granules fraction. OPLS models with good predictive properties (Q^2>0.7) were built from the NIR spectra of pulverization phase for the real time monitoring of loratadine and PVP granule layering. Granule properties (% of sieve fraction size, PVP% and granule flowing properties) were predicted using models built on NIR spectral data from the drying phase of the process.

CONCLUSIONS: This work demonstrates the de way of applying Multivariate Data Analysis with Quality by Design paradigm for process understanding and product quality control of mannitol based granulates loaded with loratadine by solution layering

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P2C-9

Texture assessment and multivariate data analysis: development of a predictive model for oral disintegration profile and palatability of orodispersible tablets

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BACKGROUND: Among patient-centered dosage forms, orodispersible tablets were easily accepted both by patients and pharmaceutical industry, often as replacements for conventional tablets. Their development involves *in vivo* disintegration and palatability testing on healthy volunteers. Texture analysis was previously used to estimate oral disintegration time, with promising results.

AIMS: The aim of this study was to develop a predictive model to correlate texture analysis of orodispersible tablets with the oral disintegration time and

mouthfeel, by means of multivariate data analysis (MVDA).

RESULTS: Placebo tablets were prepared according to an experimental design, by wet granulation. High formulation diversity regarding disintegration time and mouthfeel was achieved using two superdisintegrants with different mechanisms, two fillers (mannitol and microcrystalline cellulose), two sweeteners (aspartame and sodium saccharine) and the granules were prepared at two levels of the average size (350 μm and 650 μm). The classical pharmaceutical evaluation targeted the measurement of weight uniformity, mechanical strength (between 28.60 ± 4.74 N and 38.80 ± 2.89 N), friability, disintegration time (between 7.00 ± 1.09 s and 147.83 ± 19.97 s), wetting time and water absorption ratio. *In vivo* evaluation on healthy volunteers revealed disintegration times between 34 s and 102.93 s and an exhaustive description of the palatability. Texture analysis plots of the load vs. time were recorded and their shape and surface were found as good indicators of *in vivo* tablet softening and disintegration behavior. Predictive models were developed using Partial Least Squares regressions for disintegration time, sweet taste, volume of residue and palatability (R^2 = 0.978, 0.978, 0.994 and 0.99, respectively).

CONCLUSIONS: The study achieved the prediction of the most important subjective characteristics of orodispersible tablets disintegration using an instrumental method and MVDA.

P2C-10

Design and development of multivitamin tablets with Quality by Design approach

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BACKGROUND: The aim of pharmaceutical development is to provide the safety, efficacy and quality of the product. Instead of the traditional Quality by Testing method a new approach, the Quality by Design (QbD) is preferred nowadays. In this risk based method the critical parameters which have significant influence ont he safety and quality of the product are defined right at the beginning of the development. It can be especially useful by such complex formulations like multivitamin tablets.

AIMS: The aim of this study was to design and formulate a multivitamin tablet for direct compression, using the QbD approach, to find the optimal parameters for production and composition and to define the Design Space of the tablets. As model active ingredients water- and fat soluble vitamins were selected.

RESULTS: All information from the literature and from preformulation studies were collected for the knowledge space development. Then the design and development process was performed by the QbD method. The Quality Target Product Profile was defined and the critical factors (Critical Quality Parameters and Critical Process Parameters) were selected. According to the Risk Assessment (RA) results, factors of factorial design were selected. These were the amount of the fat soluble vitamins and compressing force. In the Design of Experiments phase 9 tablet samples were produced and examined and the Design Space was defined, namely ranges of the critical parameters where the quality of the product is suitable.

CONCLUSIONS: In this study the QbD method was successfully used in multivitamin tablet development, which is a complex task with technological challenges. The QbD based prospective process resulted in an abbreviated but effective development and it is useful by formulations with high diversity in composition (many components, chemical complexity, different ranges in dosage etc.)

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P2C-11

Development and validation of NIR spectroscopic method for simultaneous quantification of paracetamol and caffeine in tablets

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BACKGROUND: The Guidance for Industry implemented by FDA starting with 2004 encourages the voluntary development of innovative pharmaceutical technologies based on Process Analytical

Technology (PAT). In the last decade the Near Infrared Spectroscopy (NIRS) became a widely used technique for direct and non-destructive analysis of solid samples as a PAT tool.

AIMS: The objective of this work was to develop and validate a NIRS method for direct and simultaneous quantification of paracetamol and caffeine in intact tablets.

RESULTS: The calibration model was developed based on the NIR transmission spectrum recorded on 28 series of intact tablets samples prepared according to an experimantal design with 2 factors and 5 levels. The best predictive model for paracetamol was developed using standard normal variate pre-processing method and 2 PLS factors; the best predictive model for cafeine was developed using first derivate followed by standard normal variate pre-processing method and 7 PLS factors. The method was validated in terms of trueness, precision and accuracy and the results showed that the developed method is appropriate for prediction of paracetamol (ranging from 270 to 330 mg/tablet) and caffeine(ranging from 27 to 33 mg/tablet) on intact tablets witout any sample preparation. Furthermore, the APIs content in tablets was determined by means of NIRS-chemometric methods and HPLC reference methods. A good correlation between predicted and determined results was found, the differences being statistically insignificant and total prediction errors were under ± 5%.

CONCLUSIONS: Considering the obtained results, the NIR spectrosopy proved to be a suitable tool for direct and simultaneous quantification of the chemical composition regarding the APIs content of tablets with paracetamol and caffeine. Such quick NIRS – chemometric method can be used for in line/at line monitoring of the manufacturing process of fixed dose combinations tablets with paracetamol and caffeine and is useful in achieving the goals of the PAT concept.

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P2C-12

Applying the principles of quality by design coupled with multivariate data analysis in establishing the impact of raw material variability for extended release indapamide tablets

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BACKGROUND: The raw material is considered a source of variability, however the conventional, empirical development approach does not offer much information regarding the critical attributes and how processes can be modulated as to remain in the constant quality region.

AIMS: The objective of the study was to develop extended release hydrophilic matrix tablets with indapamide based on the quality by design concept, evaluating the impact of interchanging different types and suppliers of raw material on the finished product quality profile.

RESULTS: Results showed significant variability within the in vitro release tests, the root cause being traced back to the API. The investigation was extended as to characterize the material from different physicochemical perspectives and using the multivariate data processing technique it was able to establish a network that can explain the global phenomena.

CONCLUSIONS: Applying small, inevitable changes within the raw material proved to impact the final product quality, highlighting the need to establish a risk based control strategy for the supplied materials. The impact of the raw material is complex, resulting from the simultaneous action of different physicochemical properties, suggesting that the current approach of material selection and specification establishment should be reconsidered as to include a multivariate data analysis.

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P2C-13

Continuous twin screw melt granulation and real-time imaging as a potential PACT tool

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BACKGROUND: Continuous manufacturing combined with real-time analytics and process control might be the new standard for newly developed pharmaceutical manufacturing processes in the next decades which is highly promoted by the authorities besides to the big pharma companies. [1] The academia must support these efforts by developing new, innovative continuous technologies, real-time analitics and real-time control strategies to achieve Process Analitically Controlled Technologies (PACTs).

AIMS: The first aim of this study is to develop a continuous granulation method without the use of water of organic solvent based on melting of excipient(s) during the process which can act as a granulation liquid. The other aim was to map the capabilities of real-time imaging combined with real-time image analysis for process monitoring and feedback control of contiunuous granulation as a PACT tool.

RESULTS: Solvent-free continuous melt granulation and tableting experiments were conducted using a twin screw QuickExtruder as a continuous melt granulator and a Dott Bonapace excentric tableting machine. Caffeine as a model API and lactose as filler were granulated using PEG as granulating material which melts over 60°C and agglomerates the particles to form granules with larger size and better flowability than the unprocessed mixture. After the granulation process the flowability and the tabletability of the caffeine containing mixture were improved significantly from an untabletable powder mixture to a well tabletable granule. Owing to the solvent-free granulation process there was no need for the time-, space- and energy-consuming drying of the granules. In-line imaging with the developed real-time image analysis can provide valuable information about the particle size distribution, the particle shapes and the change of them during the process. The obtained information can be a good base of the real-time control of the process.

CONCLUSIONS: Continuous melt granulation is a promising solvent-free granulation alternative with several considerable advantages (e.g. solvent-free, drying-free, continuous). Real-time imaging combined with real-time can be a good development tool for process understanding and can be used for process control as well.

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P2C-14

Improving protein product quality through real-time bioprocess control based on raman spectroscopy

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BACKGROUND: The quality of therapeutic CHO cell culture proteins is a result of the entire production process. Producing therapeutic proteins with consistent characteristics is a challenging task which requires a high level of process understanding and maintaining process conditions within an optimal batch trajectory.

AIMS: The aim was to enable - via *in situ* Raman spectroscopy - simultaneous monitoring of multiple product quality relevant parameter and allowing for in-process corrections.

RESULTS: Process development, pilot, and manufacturing scale CHO cell culture batches were utilized to demonstrate the feasibility of monitoring and effect of controlling multiple critical process parameters in real-time using Raman spectroscopy. Case studies in the presentation illustrate the impact of Raman based bioprocess control to the cells, the cell culture environment, the yield, and finally to the quality of therapeutic proteins [1]. Results of the case studies provide valuable insights into effective control strategies and explicate the successful transfer of analytical Raman methods from process development to GMP manufacturing.

CONCLUSIONS: Precise navigation and smart adaptation of critical upstream process conditions based on Raman spectroscopy reduced the complexity of producing high quality products.

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P2C-15

Application of Quality by Design in orodispersable tablets development

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BACKGROUND: The actual concern of pharmaceutical product development relies on ensuring an adequate product quality through an effective process. Quality-by-Design (QbD) concept was introduced in drug formulation and development in order to achieve a good process understanding and to identify variability sources that influence the product features, respectively to build quality from development stage.

AIMS: The current work had the main purpose to develop and characterize orodispersable tablets containing ibuprofen, obtained through lyophilisation. Risk assessment evaluation was applied for this experiment. With a D-optimal experimental design with six factors and two levels, twenty-five experimental formulations were prepared with the intent to evaluate the formulation factors that influence the desired quality target product profile (QTPP): disintegration time, wetting time, mean dissolution time, texture and bio-adhesive features of the orodispersable tablets.

RESULTS: The main observations are the following: the type of the matrix forming and bio-adhesive agent influenced the disintegration time. All formulation factors had influences on the wetting time, while no significant influence was observed for the bio-adhesive properties of the tablets. The hardness and rigidity of the tablets was increased by gelatine, while the methylcellulose and xanthan gum conducted to opposite results. The fracturability of the tablets was influenced only by the quantitative factors, respectively the percentage of the matrix forming agent and the bio-adhesive agent. The dissolution profile was slightly influenced by the type of bio-adhesive agent. Based on data analysis, the conditions for an optimum formulation were defined.

CONCLUSIONS: The obtained results represent a contribution in understanding the preparation and formulation processes of orodispersable dosage forms. According to the results orodispersable tablets with ibuprofen for paediatric use with desired pharmaceutical characteristics may be successfully obtained by lyophilisation.

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POSTER SECTION 2D PHARMACEUTICAL TECHNOLOGY 3

P2D-1

Macro- and microstructural tracking of preformulation and ageing-related changes of papaverine hydrochloride-loaded electrospun nanofibrous buccal sheets

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BACKGROUND: Papaverine hydrochloride has a non-specific direct relaxant effect on smooth muscles. One of its therapeutic indications is cerebral ischemia, but some unfavorable properties confine its clinical applicability. A nanofibrous buccal formulation can improve the oral bioavailability of the drug as a result of the enhanced solubility and lack of the first pass metabolism. The intra-and inter-individual variability can also be decreased as well.

AIMS: The aim of this study was to prepare papaverine hydrochloride loaded buccal nanofibrous sheets and to determine the optimum composition of hydroxypropyl cellulose (HPC) - poly(vinyl alcohol) (PVA) gels (with 15 %(w/w) total polymer concentration) for electrospun fiber formation with the combination of rheological, molar reflectance, and scanning electron microscopy measurements (SEM). The further aim was to track the solid state changes relating to the stress induced physical ageing of the best composition system. Micro- and macrostructural alterations were detected using Raman-, positron annihilation lifetime- and Fourier transform infrared spectroscopy and SEM.

RESULTS: Correlation was found between the micro- and macrostructural properties of the gels and their electrospinnability. Gels of the lowest

elasticity and slightest intermolecular interactions and the more ordered intramolecular structure contributed to the best fiber characteristics of the samples. During the stability test significant changes were revealed at both supramolecular and macroscopic levels. Two-step ageing process of the drug carrier and a partial phase transition of the active were observed.

CONCLUSIONS: The combination of micro- and macrostructural characterization of the gels and the electrospun samples is an effective way to achieve the optimum characteristics and follow the physical stability of the formulation.

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P2D-2

The effect of dilution and temperature on the viscosity of various ocular lubricants

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BACKGROUND: The main limitation of current ocular lubricants is the short duration of symptom control. An alternative approach is to use lubricants with high viscosity.[1] The viscosity of eye drops required to maintain precorneal residence has been reported to be in the range 15 – 150 mPa·s.[2]

AIMS: To investigate the effect of dilution and temperature on the viscosity of ocular lubricants prepared using various viscosity modifiers. Compounded ophtalmic vehicles containing Hypromellose (HPM) 0.3 %, MMW chitosan (CS) 1 %, hydroxypropyl guar gum (HP GG) 0.5 %, CS 0.5 %/HP GG 0.25 % and commercial eye drops (Hemodrops® (containing HPM 0.5 %), Systane® Ultra Lubricant (SU), and Systane® Gel Drops (SGD) (both containing HP GG)) were investigated. The viscosity measurements were performed using a rotational rheometer at 20 and 34 °C (after addition of the simulated tear fluid (pH 7.4) in a ratio of 40:7).

RESULTS:The obtained results showed decrease in viscosity of compounded eye drops of about 2-fold i.e. from 14.15 to 8.85 mPa·s (for HPM 0.3 %), 86.45 to 38.15 mPa·s (for CS 1 %), 91.45 to 52.5 mPa·s (for HP GG 0.5 %) and 49.25 to 24.35 mPa·s (for CS 0.5 %/HP GG 0.25 %). An increase in viscosity (from 2.7 to 19.1 mPa·s) was observed only for commercial (SU) drops. The highest values of viscosity were revealed for SGD sample (216 i.e. 136 mPa·s) under the stated experimental conditions.

CONCLUSIONS: The simultaneous increase of temperature and dilution of the prepared ocular lubricants induced changes in viscosity for all the samples. The samples containing CS and HP GG (alone or in combination) have shown higher starting values of viscosity and after the exposure to the stated experimental conditions, compared to the samples containing HPM. The viscosity of all the studied ocular lubricants was in the range recommended for topical ophthalmic preparations.

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P2D-3

Stability study of acetylsalicylic acid during pharmaceutical operations

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BACKGROUND: The Acetylsalicylic acid (ASA) is known to be sensitive towards moisture heat and pH changes[1] . The stability studies constitutes a decisive element during pharmaceutical developpement and guarantees quality of the product, which is the aim of this study.[2]

AIMS: The aim of this work is to study the stability of the Acetylsalicylic acid during fabrication and for pH changes.In one hand the degradation of the ASA was tested during pharmaceutical operations such as, milling, compression and mixing, which can generate a rise in temperature . And in the other hand, l'ASA was treated with chloridric acid and sodium hydroxid solutions with differentes concentrations varing beween 0.5 and 3 M, in order to test the effect of the pH change on the ASA stability.

RESULTS: The ASA degradation was observed during milling at three speed levels (150, 350 and

700 RPM) for 1 hour. The ASA degradation is more pronouced at 150 RPM, where 13% of degradation was obseved compared to 7% of degradation at 350 and 700 RPM. The addition of 10% of microcristallyne celluloce pH 102 during milling can reduce the drug degradation. The degradation was not observed either during compression or mixing. The acid treatment of ASA caused a degradation of 4%, against the basic treatement caused a degradation of 10%.

CONCLUSIONS: From this study it can be conclude that the milling operation cause ASA degradation resulting from the rise in temperature and the active ingredient can be protected during milling operation by adding the microcrystalline cellulose pH102, which be used as filler in the formulation. The ASA in more sensitive to the basic pH changes then the acid ones.

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P2D-4

Monitoring the stability and physichochemical changes of Suspensio anaesthetica

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BACKGROUND: Suspensio anaesthetica is an official formulation of Formulae Normales Editio VII. used in the treatment of oncological patients for the anesthesia of the mouth, the throat, and the esophageal mucosa. The active substance, benzocaine belongs to the group of local anesthetics, which can be found in a suspended form in the magistral preparation because of its low aqueous solubility. Swallowing the product often causes difficulties for oncological patients, especially for those who suffer from head and neck cancer. The major issue surrounding this formulation lies in the high viscosity resulted from the use of hydroxyethylcellulose. Most of the patients prefer a drug with „water-like" consistency.

AIMS: The aim of our research was to prepare suspensions of reduced Mucilago hydroxyaethylcellulosi content to facilitate the administration of the medicine for oncological patients with swallowing difficulties.

RESULTS: As a result of the reduced amount of thickening agent, the preparations did not meet the zeta potential requirements. At the end of the 4-week long storage period, the average particle sizes increased, the viscosity decreased, however the redispersability was retained.

CONCLUSIONS: On the basis of the results we can state that the formulations tested do not have adequate physical stability. Zeta potential values and particle size characteristics clearly indicate that the stability of the composition is negatively affected by the reduction of Mucilago hydroxyaethylcellulosi. Although, the lower the amount of Mucilago hydroxyaethylcellulosi, the lower the viscosity, in accordance with the hypothesis, further stability tests are required.

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P2D-5

Importance of freeze-thaw studies in biopharmaceutical development

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BACKGROUND: Biopharmaceutical drug product quality should be controlled throughout manufacturing, storage, transportation, and delivery to the patients. Storage conditions are defined during stability studies in accordance with the ICH/WHO guidelines, but manufacture and transport are not covered by these guidelines. Additional such freeze-thaw studies are necessary to gather a full dataset in relation to the product's stability profile.

AIMS: Freezing of bulk protein solutions prior to drug product manufacture is common in the biopharmaceutical industry. Freezing allows for prolongation of protein drug substance shelf life. However, freezing and thawing may cause changes in the chemical and physical properties of biopharmaceutical product solutions. The objective of the study was to determine the impact of several freeze-thaw cycles on product stability.

RESULTS: Several analytical methods such as Reverse Phase (RP), Size Exclusion (SE), Ion Exchange chromatography (IEX), Micro-Flow Imaging (MFI), Capillary gel electrophoresis (CGE), Circular dichroism (CD) spectroscopy and other physical characterization methods were used to analyse protein stability after freeze/thaw cycles.

CONCLUSIONS: Based on the results from

these carefully selected analytical methods, insights were drawn on the impact of freeze-thaw stress on the product stability of certain biopharmaceutical proteins.

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P2D-6

Evaluation of biocompatible polymer gels before and after freeze drying

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BACKGROUND: Freeze drying offers many advantages in pharmaceutical technology. The prolonged physical, chemical and microbiological stability thanks to low moisture content ensures a long shelf-life. The product is porous and has high specific surface area, so it offers improved dissolution rate. Freeze drying is used for formulation of injections, infusions, transfusions, vaccines and orally disintegrating tablets as well as for wound dressings or contact lenses containing drugs[1]. Hydrophilic polymers like chitosan, sodium alginate, hyaluronic acid, locust bean gum and Carbopol® polymers are biocompatible gelling substances for these lyophilized products[2].

AIMS: The aim of this study was to evaluate biocompatible polymer gels before and after freeze drying, comparison of the polymers above.

RESULTS: Chitosan gels were prepared by dissolving chitosan in different organic acids. Sodium alginate gels were made using purified water, as well as the locust bean gum and Carbopol® gels. Rheological properties of the gels were investigated using Kinexus Pro rheometer. The gels were lyophilized in a Scanvac Coolsafe™ freeze dryer. Water content was determined by Karl-Fischer method using Metrohm 787 KF Titrino autotitrator.

CONCLUSIONS: The polymers can be lyophilized to obtain a dry, porous structure with prolonged stability. The freeze-dried gel samples showed gelling ability after reconstitution. The rheological properties of gels are appropriate to formulate freeze dried drug delivery systems.

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P2D-7

Evaluation of potential compressing of the microspheres containing losartan potassium

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BACKGROUND: Microspheres are one of the drug forms which can provide prolonged release of the active substance. They are monolithic, porous or smooth micropellets, sized from 1 to 500 μm.

AIMS: In the present study we aimed to analyze the possibility of compressing microspheres with losartan potassium. Losartan was selected for the study due to its low bioavailability (33%) and short half-life in the human body (2h).

RESULTS: For the preparation of microspheres containing losartan potassium on the Eudragit L30D55 matrix, the method of spray drying was used. The tablets were prepared by direct compression using the ERWEKA AR400 tablet press with 6 mm punches and a pressure force of 8kN. Five series of tablets containing microspheres with LOS:EUDRAGIT ratio of 1: 1 and 10% methylcellulose, 30% methylcellulose and mannitol as a filler were made. To assess the presence of microspheres in the manufactured tablets the pictures of the tablets were also made using Scanning Electron Microscope (SEM, SUPRA25 Carl Zeiss company). The analysis of the photos justifies the fact that with the increasing amount of methylcellulose, the homogeneity of the surface increases as well as the more concentrated tablet surface is observed. Compared to the standard (microspheres Los:Eu 1:1), microspheres contained in tablets have smaller particle size and less spherical morphology.

CONCLUSIONS: Based on the performed studies we can conclude that the microspheres of losartan potassium with the size not exceeding 3.5 μm do not deform during compressing while the larger microspheres are deformed and/or lost in the analyzed material.

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P2D-8

Atenolol ointment stability

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BACKGROUND: Atenolol is a known drug and it has been used for a number of years in the treatment of cardiovascular diseases. For the purpose of testing potential local anti-inflammatory activity of beta blocker containing ointments, a 1% atenolol ointment in the fatty carbohydrate medium was prepared. The ointment was tested for stability. Evaluations for physical and chemical stability were performed initially and throughout the storage period of six months.

AIMS: The aim of the study is prepare and testing stability of the 1% atenolol ointment prepared in the fatty carbohydrate medium.

RESULTS: Testing of the stability of the samples of finished ointment stored at the temperature of 25°C and relative humidity of 60% and the temperature of 40°C and relative humidity of 75% was performed with two analytical methods: UV spectroscopy and high pressure chromatography. By comparing the results obtained from these two methods no differences of the said content were observed. The samples stored according to ICH guidelines did not show significant degradation. In the tested ointment the atenolol content is within the limits prescribed in monographs for ointment (95,00 to 105,00%) in accelerated test on 40°C, as well as in long-term test at 25°C, over a period of 6 months. The content of degradation products did not exceed the values of 0,04 for individual related substance.

CONCLUSIONS: The pre-formulation tests have shown a satisfactory quality of atenolol ointment in which this substance has been incorporated. Atenolol is compatible with a fatty medium used for production of 1% atenolol ointment. It has been established that the ointment is stable for at least a year if it is kept at the temperature up to 25°C, i.e. at least six months at the temperature up to 40°C.

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P2D-9

HPLC determination of benzaldehyde in benzyl alcohol containing injectable formulations

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BACKGROUND: Benzyl alcohol is frequently used as a bacteriostatic agent or cosolvent in a variety of liquid pharmaceutical preparations. It can easily undergo oxidative degradation to benzaldehyde and benzoic acid. The presence of these potential impurities needs to be checked owing to its reactivity and toxicity (neurotoxic and allergic reactions) [1].

AIMS: The purpose of this work was to adapt and use the HPLC method proposed by Tan et al. for the assay of benzyl alcohol, benzaldehyde and benzoic acid in injectable formulations commercially available from the local market [2].

RESULTS: A total of 10 different injectable products containing benzyl alcohol were analysed using a Shimadzu LC10-Avp system, equipped with a DAD detector, auto-injector (20 μL) and a Zorbax StableBond C18 column (250 X 4.6 mm, 5 μm), at 25°C. HPLC was performed with an isocratic mobile phase composed of water-acetonitrile-glacial acetic acid (760:240:5, v/v/v, pH 2.5) and peaks were detected at 254 nm. Flow rate was 2.0 mL min-1. The new and simple HPLC assay method was validated for linearity (r> 0.99927), precision (repeatability: RSD< 0.96%; intermediate precision: RSD< 0.97%), accuracy (Rc= 98.76-101.22%) and specificity. Established HPLC method proposed for selective quantitation of neurotoxic benzaldehyde is suitable for application to the quality control analysis of benzyl alcohol containing injection formulations. The results showed that three of the generic brands contained considerable amounts of the toxic benzaldehyde (>0.05% of the benzyl alcohol content).

CONCLUSIONS: The developed HPLC method can be used to quantify benzaldehyde in injectable formulations. The finding that some injectable formulations contain higher than acceptable levels of benzaldehyde, illustrates the need for stringent quality control in the manufacture of these solutions.

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P2D-10

Comparison of pharmaceutical technological parameters of pharmaceutical equivalents

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BACKGROUND: Ranitidine hydrochloride is commercially available as a generic drug. Pharmaceutical equivalents may vary in their pharmaceutical technological characteristics due to the application of different technological parameters in the production process, as a result of different excipients used in generic drugs production.

AIMS: In this study, we compared pharmaceutical technological characteristics of two generic drugs of ranitidine film coated tablets (*tablets 1 and tablets 2*) from different manufacturers, which are available on the market of Bosnia and Herzegovina. Both generic drugs contain ranitidine hydrochloride, but different excipients in tablet core and film coating.

RESULTS: Tablets have been evaluated using the same pharmaceutical technological tests (uniformity of dosage units, assay, dissolution test, friability test, disintegration and hardness testing) to determine whether the obtained data fulfill pharmacopoeial requirements. The results of uniformity of dosage units, assay, friability testing and disintegration time of tablets for both generic drugs meet pharmacopoeial requirements. Significant variations were observed in hardness testing for *tablets 1* compared to hardness testing for *tablets 2*. Tested pharmaceutical equivalents may be considered bioequivalent because of *in vitro* dissolution testing of ranitidine tablets.

CONCLUSIONS: Based on pharmaceutical technological characterization of ranitidine film coated tablets, *tablets 2* would be drug product of choice. Because of lactose intolerance, *tablets 2* can not be used in all patients.

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P2D-11

Detection of interactions between active substance and excipients used in the formulation of lisinopril coated pellets using differential scanning calorimetry

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BACKGROUND: Pellets are very popular solid dosage form, since they have numerous therapeutical and technological advances. Their spherical shape and smooth surface make them ideal substrate for coating, in order to achieve controlled release of active substance. If the active substance is highly water soluble it can migrate into the coating layer and lead to faster release rates. Mentioned migration can be a consequence of interaction between active substance and excipients used in formulation.

AIMS: TG/DSC investigation of the thermal behavior of lisinopril coated pellets and possible interactions between the active substance and excipients, that may occur during the processing of pellets.

RESULTS: DSC thermograms of lisinopril coated pellets show broad endothermic peaks, of the active substance, but shifted towards higher temperatures. No peaks characteristic for excipients can be observed in the DSC thermograms of lisinopril coated pellets. There can be seen a broad exothermic peak, not present in DSC thermograms of any of the materials used.

CONCLUSIONS: The thermal analysis of lisinopril coated pellets shows that there are no interactions between active substance and exipients. Exothermic peak present in DSC thermograms of coated pellets may be attributed to partial solubilization of the active substance in water during the DSC analysis.

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P2D-12

Rheological profiling of sunscreen formulations – influence of main emulsifier and thickener

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BACKGROUND: Rheological measurments offer an insight into internal structure of non-Newtonian fluids, like liquid and semisolid preparations. Rheological properties of cosmetic products are crucial in their manufacturing as well as performance.

AIMS: Investigation of the influence of main emulsifier and the presence of a thickener on rheological properties of sunscreen emulsion formulations.

RESULTS: Four sunscreen lotion formulations were developed containing anionic emulsifier potassium stearate (formulations A1 and A2) or nonionic emulsifier glyceryl stearate/behenate (formulations N1 and N2) as a main emulsifier. A1 and N1 contained thickener Carbopol 940, while A2 and N2 did not. The rheological profiles of the formulations included: steady state viscosity, yield point, tixotropy, oscillatory amplitude sweep and oscillatory frequency sweep. All formulations showed non-Newtonian pseudoplastic flow. Formulations with anionic emulsifier had higher yield points. Formulations containing thickener showed higher yield points. However, A1 had much higher increase of yield point compared to N1. All formulations showed low tixotropy. The hysteresis loop areas are larger in formulations containing thickener, and in formulation A1 it is manifold larger than in N1. Dynamic oscillatory sweeps of the formulations showed that the phase angle was constant and low, complex viscosity decreased logarithmically, elastic modulus (G') was higher than viscous (G'') and moduli were parallel. These characteristics imply internal gel-structure of the formulations.

CONCLUSIONS: Rheological characteristics of the formulations indicate pseudoplastic systems of structured emulsions that have stable inner gel stucture at rest. Small hysteresis loop areas imply fast recovery of the initial structure, thus creating homogenous film on the skin surface that will serve its purpose in sun protection.

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POSTER SECTION 2E BIOPHARMACY

P2E-1

Melatonin: release studies from electrospun nanofiber matrices for *per os* administration

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BACKGROUND: Sleep problems are common, particularly among the elderly. Current hypnotic drugs are recommended only for short-term treatment of insomnia, but concerns about "hangover" effects and problems upon withdrawal persist. Melatonin, a hormone synthesized and released from the pineal gland at night, has been shown to have a hypnotic effect in humans. During the last decade, we have developed novel pharmaceutical formulations suitable for treating sleep onset and sleep maintenance dysfunctions [1].

AIMS: Targeting at mimicking the physiological release of melatonin, we report herein on its release profile in aqueous media from capsules loaded with electrospun nanofiber matrices [2] incorporating melatonin.

RESULTS: The results from the *in vitro* release experiments suggest that at pH 1.2, melatonin is almost instantaneously released from melatonin-loaded nanofibers, thus promoting sleep onset. Interestingly, melatonin's release after this initial burst becomes well regulated at pH 6.8, exhibiting an ideal dissolution profile for dealing with poor sleep maintenance.

CONCLUSIONS: The electrospun nanofibers used in this work are promising drug delivery systems for the *per os* administration of melatonin.

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P2E-2

In vivo performance study of fast inverted oil-in-water emulsion and reference oil-in-water emulsion with incorporated dihydroquercetin

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BACKGROUND: SWOP (*Switch-Oil-Phase*) emulsions are fast inverted oil-in-water (o/w) emulsions which invert into water-in-oil emulsions when applied to the skin (1). Dihydroquercetin (DHQ) is used in cosmetics as an antioxidant and shows absorption in the ultraviolet spectrum (2). Thus incorporation of DHQ into SWOP emulsion could result in new waterproof sun protection product.

AIMS: The SWOP (SE) and the reference o/w (ROWE) emulsions without DHQ and with 5% of DHQ (F1 and F3, respectively) were prepared to estimate their different effects on the skin. For that purpose, an *in vivo*, short-term study which included measurements of transepidermal water loss (*TEWL*), *stratum corneum* hydration (*SCH*), skin's pH (pH) and the erythema index (*EI*) was performed.

RESULTS: There were no statistically significant changes at any time point in *SCH* and *TEWL* values for any sample. Nevertheless, 1 hour after application, the sample SE showed the highest trend of increase in *SCH*. Furthermore, a trend of *TEWL* increase was noticeable after o/w emulsion application, and the results for SE and F1 samples were similar to the non-treated control. No changes in the pH and *EI* values were noticed after the emulsions application. A specially designed 2-min study was performed on F1 sample to observe possible effects of the SWOP emulsion on *SCH*, due to its inversion. It was determined that *SCH* was statistically increased comparted to the basal values even 20 s after application. However, 1 min after application, *SCH* levels returned to the basal values without further changes.

CONCLUSIONS: An *in vivo* performance study indicated better hydrating potential of the SWOP compared to the o/w emulsion. Additionally, emulsions with DHQ did not change the skin pH and *E*I values, which implys satisfactory irritation potential. The obtained results of *SCH* levels revealed fast inversion of the SWOP emulsion.

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P2E-3

Antibacterial activity and safety testings of differently designed electrospun matrices for periodontal diseases

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BACKGROUND: Patients with periodontal diseases, caused by different bacteria (1), are often prescribed antibacterial agents to avoid infection development. It is a great challenge to deliver the drug locally into periodontal pockets. One solution would be to use electrospun drug-loaded fibrous matrices as delivery systems for antibacterial agents locally.

AIMS: To prepare electrospun drug-loaded matrices and understand their antibacterial activity and safety for dental applications.

RESULTS: Electrospun nanofibrous matrices based on poly(ε-caprolactone) (PCL) together with different antibacterial agents metronidazole (MTZ) and ciprofloxacin HCl (CPR) were successfully designed and investigated for their drug release, antibacterial activity and safety. Antibacterial activity testings by agar diffusion were performed in aerobic as well as anaerobic conditions which allowed revealing the effectiveness of developed matrices. Pathogenic bacterial strains important for periodontitis showed different antibiotic sensitivity against MTZ and CPR released from drug-loaded matrices. Combination matrices consisting both MTZ and CPR showed the inhibition of bacterial growth against all tested bacterial strains, CPR was more effective against Actinomyces weissii and MTZ against other anaerobic bacteria (eg Fusobacterium nucleatum subsp. polymorphum). All tested matrices were non-toxic to normal baby hamster kidney fibroblast cells .

CONCLUSIONS: Combined metronidazole (MTZ) and ciprofloxacin (CPR) loaded electrospun matrices are biocompatible and useful for the prevention and treatment of periodontitis. For the periodontitis treatment it is important to investigate the activity of drug-loaded matrices on both aerobic as well as anaerobic relevant pathogenic bacterial strains.

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P2E-4

Enhanced skin penetration of tacrolimus and fusidic acid from nano-sized colloidal carriers

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BACKGROUND: Tacrolimus and fucidic acid are highly lipophilic compounds used in topical treatment of atopic dermatitis. In order to improve skin penetration of drugs nano-sized colloidal systems, namely microemulsions are widely used as topical carriers (1).

AIMS: The aim of this work was to formulate microemulsions of both tacrolimus and fusidic acid and to examine skin uptake of these drugs from the optimized formulations.

RESULTS: Microemulsion components were consisted of Capryol 90 (oil phase), Labrasol (surfactant), Transcutol P (co-surfactant) and water. In vitro penetration of both drugs across pig skin from microemulsions was significantly enhanced (up to 2.15 fold for tacrolimus and up to 1.86 fold for fusidic acid) compared to their marketed ointment and cream formulations. ATR-FTIR analyses revealed the interactions between skin lipids and microemulsion components. CLSM studies demonstrated the extension and depth of skin penetration of a model lipophilic fluorescent dye from the optimised microemulsion.

CONCLUSIONS: Microemulsions could be a potential topical carrier to improve the skin uptake of both tacrolimus and fusidic.

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P2E-5

Dissolution improvement of poorly water soluble model drug albendazole with surfactant assisted media milling process

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BACKGROUND: Milling involves the application of mechanical energy to physically break down coarse particles to finer ones and is regarded as a "top–down" approach in the production of either micro-, either nanoparticles[1]. These particulates are mainly desired for the formulation of parenteral, respiratory and transdermal drug delivery systems. During a milling process we can improve the solute drug's dissolution rate can be improved, by increasing its surface area and decreasing the thickness of the diffusion barrier.

AIMS: The purpose of this study is to create nanosuspensions from the model drug albendazole, which is a poorly water soluble BCS class II. drug, optimize the affecting factors of the surfactant assisted wet-milling process (milling speed, process time, different beads to powder ratios, types of different milling medias, different volumes of the milling containers, different surfactant types and concentrations)[2]. The optimized formula was then added to solid carriers and dried. Both reconstitution from the solid carrier, dissolution profile studies were investigated in artificial rumen fluid and compared to the unmilled dispersion to demonstrate the efficiency of the milling process.

RESULTS: Reconstitution studies demonstrated that, the released API's PSDs are in the nano range. Surfactant assisted media milling significantly improved the dissolution rate and water solubility of albendazole.

CONCLUSIONS: Surfactant assisted media milling is an effective technique to improve dissolution rate and water solubility of drugs, but we have many challenges to overcome, due to the several variable parameters influencing the process.

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P2E-6

Improvement of solubility, dissolution rate and bioavailability of cilostazol using different technique of solid dispersion

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BACKGROUND: Solid dispersion is containing at least two different components one is hydrophilic

matrix and another is hydrophobic drug. Amorphous products and particularly amorphous solid dispersions are currently one of the most exciting areas in the pharmaceutical field. This approach presents huge potential and advantageous features concerning the overall improvement of drug bioavailability. Currently, different manufacturing processes are being developed to produce amorphous solid dispersions ranging from solvent evaporation to melting processes[1,2].

AIMS: The aim of this study was to improve dissolution rate, water solubility and stabilize amorphous form e.g. Cilostazol (CLZ) through formulation of binary and ternary solid dispersion systems (SDs) using different carriers and surfactants by different techniques, solvent evaporation and fusion approaches. The prepared binary and ternary SDs were characterized using different imaging and spectroscopic methods, in vitro dissolution studies and physical characterization of powders.

RESULTS: Both SDs made by solvent evaporation and fusion method is significantly increased the dissolution rate compared to the physical mixtures. Imaging and spectroscopic studies confirmed the crystalline to amorphous transitions. Powder physical characterization studies demonstrated that, all requirements of the Ph. Eur. 9.0 have met.

CONCLUSIONS: The above used techniques are all suitable for improving the dissolution rate and water solubility.

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P2E-7

The effect of selected terpenes on release and skin retention of quercetin from hydrogels

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BACKGROUND: Quercetin is a flavonoid providing novel possibilities for the treatment and prevention of oxidative-stress mediated skin diseases and premature skin ageing. However, quercetin skin penetration is limited and should be improved to increase skin retention. One strategy to enhance the skin retention is use of penetration enhancers e.g. terpenes.

AIMS: To assess the effect of four different terpenes (camphor, linalool, menthol, pinene) on the porcine ear skin retention and on the release of quercetin from the hydrogels in *in-vitro* conditions.

RESULTS: The significant increase in the quercetin skin retention was observed when camphor or menthol was used as a penetration enhancer. Linalool or pinene had no effect on the quercetin skin retention. None of the used terpenes affect the release of quercetin from hydrogels. The correlation between the skin retention and the release rate was not observed.

CONCLUSIONS: The effect of the chemical structure of terpenes on the skin retention of quercetin was reported. The most effective skin retention enhancement was achieved with cyclic terpenes containing oxygen atom (menthol or camphor). The acyclic terpene containing oxygen atom (linalool) or cyclic hydrocarbons (pinene) were ineffective in skin retention promotion. The mechanism of menthol or camphor skin retention enhancement is the interaction of that terpenes with the skin barrier but not the release rate enhancement.

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P2E-8

Investigating the driving force of membrane transport of Carvedilol from supersaturated solutions achieved by electrospun formulations

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BACKGROUND: When a poorly water-soluble active pharmaceutical ingredient (API) is formulated to enhance its dissolution, additives, such as surfactants, polymers and cyclodextrins have an effect not only on dissolution profile, but also on flux through the membrane[1]understanding how solute thermodynamic activity varies with solution composition, particularly in the presence of solubilizing additives, is important in the context of passive absorption.\\n\\nMETHODS: In this

study, a side-by-side diffusion cell was used to evaluate solute flux for solutions of nifedipine and felodipine in the absence and presence of different solubilizing additives at various solute concentrations.\\n\\nRESULTS: At a given solute concentration above the equilibrium solubility, it was observed that the solubilizing additives could reduce the membrane flux, indicating that the extent of supersaturation can be reduced. However, the flux could be increased back to the same maximum value (which was determined by the concentration where liquid-liquid phase separation (LLPS. In order to fully understand these effects on flux, the driving force of membrane transport cannot be simplified to the total concentration gradient.

AIMS: The aim of this study was to investigate the impact of formulation excipients, solubilizing additives and self-aggregation on dissolution, supersaturation and membrane transport of an API.

RESULTS: Carvedilol, an anti-hypertensive drug was chosen as a poorly water-soluble model drug and formulated in order to enhance its dissolution using solvent-based electrospinning. Two polyvinylpyrrolidone (PVP) derivatives (K30 and VA64) and Soluplus were used to create three different amorphous solid dispersions of the API. The effect of various additives that can influence the characteristics of dissolution and permeation through artificial membrane were observed by carrying out a simultaneous dissolution-permeation study with a side-by-side diffusion cell, μFLUX™. Results showed that all amorphous solid dispersions were effective in dissolution enhancement of the poorly water-soluble API, namely more than 90 % of the drug content was released from all formulations. Although the dissolution profiles of the formulations were found to be very similar, fluxus differed significantly in case of Soluplus and PVP containing formulations.

CONCLUSIONS: The results show that the driving force of membrane transport cannot be simplified to the concentration gradient. Supersaturation gradient, the difference in degree of supersaturation (defined as the ratio of dissolved amount of the drug to its thermodynamic solubility) between the donor and acceptor side was found to be the driving force of membrane transport.

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P2E-9

Improve stability and oral bioavailibility of Plantago lanceolata herb extract by using a Self-Microemulsifying Drug Delivery System

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BACKGROUND: Plantago lanceolata (Ribwort plantain) possesses various pharmacological effects for human health including antioxidant, anti-inflammatory, hepatoprotective immunoregulation and neuroprotective properties with an excellent safety profile.The limitation of their formulation is the poor chemical stability due to hydrolysis. SMEDDS is frequently used for the stabilization of natural product and these carrier systems may also increase the bioavailability of natural bioactive materials (Eid et al. 2014).

AIMS: The aim of this work was to formulating a SMEDDS (selfmicroemulsifying drug delivery system) of Plantago lanceolata and assessing its in vitro and in vivo potential..This study was conducted to develop SMEDDS containing Plantago L. extract to stabilize and for increasing its bioavailibitity to improve its anti-inflammatory effect. Pseudoternary phase diagrams were used to evaluate the microemulsification existence area.The basis of the formulation was the ternaryphase diagrams contained different surfactant/cosurfactants.

RESULTS: The developed SMEDDS was spontaneously forming microemulsion upon mild agitation in distillated water at 25°C. The transmittance percentage and refractive index of the formulations indicating the transparency of them. Moreover, the developed formulation has been stable for 1 month at 25°C . MTT test results showed that all the compositions were biocompatible.The results obtained from acute cytotoxicity studies show 2 of the compositions resulted in fatal consequences and these samples were eliminated from further experiments. Our in vivo ear inflammation test presents orally administered SMEDDS compositions significantly decreased ear thickness in the complete period of time compared to the untreated, positive control.

CONCLUSIONS: 8 SMEDDS compositions containing Plantago L. prepared and were characterized by Dynamic Light Scattering method. According to our in Vitro cytotoxicity assay, every composition was accepted with no cytotoxicity by the ratio of physical dilution. However, according to our in vivo toxicity studies, 2 compositions resulted in the death of mice due to high quantity of Transcutol HP and Cremophore RH40. Other compositions have not been toxic and approved for the other test of effectiveness. Ear thickness assay was measured to certify the effect of these compositions.

This work was supported by EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" project.

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P2E-10

In vitro – in vivo characterization of simvastatin-containing periodontal mucoadhesive nanoparticulate gel

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BACKGROUND: Periodontitis is a chronic inflammatory disease characterized by gingival tissue inflammation, clinical attachment loss and alveolar bone destruction. Present scientific literature on simvastatin revealed its good applicability in the field of periodontics as a local drug delivery agent due to its antiinflammatory and bone regenerative properties. Topical application of drugs directly into the periodontal pocket represents a satisfactory approach, presents many advantages, and involves the use of a controlled release device with mucoadhesive properties.

AIMS: The purpose of the work was to formulate a topical simvastatin-containing mucoadhesive periodontal gel (SVMPG) and evaluate *in vivo* efficacy regarding clinical parameters, bone healing and systemic inflammatory response in an experimental model of periodontitis in rats, and compare the effects with oral administration of simvastatin (SV).

RESULTS: The designed SVMPG formulation consisting of glyceryl monooleate and water, combined in a ratio of 3 : 1 (containing SV in a concentration of 2%) showed adequate viscosity (41672.40±68 mPa.s at 6 s^{-1}) and adhesive characteristics (a detachment force of 175±22 mN). X-ray diffraction studies revealed that the samples contains cubosomes with the faces of cubes preferential orientated parallel with surface of the holder sample. The *in vivo* studies showed that the degree of bleeding on probing as well as the dental mobility was statistically significantly lower in the group where simvastatin was administrated topically (SMV-L) comparing to the periodontitis group without treatment (PG), (0% vs. 100%, p=0.018 for bleeding and (0% vs 100%, p=0.046) for dental mobility. The experimental results showed that SV applied either topically, through the designed SVMPG, or administered by gavage reduced the local and systemic inflammatory response induced by periodontitis.

CONCLUSIONS: The results suggest that the prepared SVMPG may be favorable for topical application in periodontal therapy.

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P2E-11

Comparison of in vitro dissolution profiles of silymarin-cyclodextrin sustained release matrix tablets

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BACKGROUND: Silymarin is the active ingredient of the plant Silybum marianum. It is used in medicine for curing or preventing liver and gall diseases for thousands of years. Silymarin has a low solubility and permeability. Current pharmacotherapy means conventional dosage forms such as capsules, which result in low bioavailability.

AIMS: Our main goals through the research were to formulate matrix tablets with silymarin as active ingredient. We used different Carbopols as matrix-forming polymers. The complexation of silymarin with different β-cyclodextrins was intended to increase the solubility of the active ingredient. By achieving sustained release, our aim was to offer a better alternative than the conventional therapy.

RESULTS: We carried out MTT assay to examine the cytotoxicity of the matrix-forming Carbopols to intestinal cells, which proved the biocompatibility of the carriers. Silymarin-cyclodextrin complexes were made by physical mixture method. Tablet ingredients were homogenized in mortar after being measured. For compressing, manual bench-top tablet press was used. We carried out weight uniformity, tablet friability and hardness test, and our products were proper according to Ph. Hg. VIII.

The medium used for the dissolution tests was artificial gastric juice in the first hour and artificial intestinal juice for six hours. We took samples in every 15 minutes from the gastric and every 30 minutes from the intestinal medium. Dissolution curves were displayed using the absorbance of the samples.

CONCLUSIONS: Comparing the results of our research, we could select the Carbopol-cyclodextrin combination with the optimal drug release of the 16 different compunds. With CD complexes, we could solve more than 85% of the silymarin. The biocompatibility of our product was proven, and the technology provided much better bioavailability than the conventional silymarin therapy.

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P2E-12

Formulation and antioxidant investigation of creams containing different plant extracts

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BACKGROUND: Some plants can be incorporated into skin care products to treat conditions such as skin dryness and can function as an anti-oxidant.
AIMS: Creams were formulated from different plant extracts. Four kinds of plant extract were examined, black locust (Robiniapseudoacacia), cowslip (Primula veris), nasturtium (Centranthus) and crocus (Crocus longiflorus).

RESULTS: Each extract was previously dissolved in Transcutol and then mixed in the same o/v cream basis containing Sucrose ester SP50 as an emulgent.In vitro drug release of different compositions was assessed by Franz diffusion method (1).Creams containing black locust showed the highest diffusion amounts. DPPH Radical Scavenging Activity of plant samples were also examined, according to methodology described by Brand-Williams (2).

CONCLUSIONS: According to our measurements nasturtium showed the highest antioxidant activity.

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POSTER SECTION 2F
ANTICANCER DRUG RESEARCH

P2F-1

Betulin-conjugated gold nanoparticles with antitumor activity

SOICA, C., MIOC, M., CORICOVAC, D., TRANDAFIRESCU, C., GHIULAI, R., PAVEL, I., DANCIU, C., PINZARU, I., MOACA, A., DRAGOMIRESCU, A., POPOVICI, R. A., DEHELEAN, C.

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BACKGROUND: Gold nanoparticles exhibit large exterior surfaces and can be easily functionalized thus being adequate as highly effective drug delivery agents [1] in cancer therapy.

AIMS: Synthesis of betulin conjugated gold nanoparticles with antitumor activity.

RESULTS: Betulin conjugated gold nanoparticles were successfully synthesized and physicochemically analyzed. Their biological activity was tested against the A375 (human melanoma) tumor cell line using the pure compound as reference. Tests revealed a higher antiproliferative activity as a result of the betulin bioconjugation.

CONCLUSIONS: Betulin bioconjugation with gold nanoparticles leads to an improved antitumor activity therefore representing a suitable option in drug delivery.

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P2F-2

Hollow gold nanoparticles loaded with betulin as anticancer agents

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BACKGROUND: Hollow gold nanoparticles (HGN) display excellent properties in terms of biocompatibility and drug loading which makes them suitable carrier molecules for a variety of drugs used in cancer therapy [1]. In addition to an optimized therapeutic activity of the loaded drug, HGN also proved superior to other drug delivery systems such as liposomes [2].

AIMS: Synthesis followed by physico-chemical and biological analysis of hollow gold nanoparticles loaded with betulin as anticancer agent.

RESULTS: Hollow gold nanoparticles were successfully synthesized by consecrated methods and physicochemically analyzed. Betulin was loaded as active antitumor agent and the resulting nanoparticles were in vitro tested against A375 (human melanoma) cell line using the pure drug as reference. Hollow gold nanoparticles revealed a high drug load and improved antitumor activity compared to betulin alone.

CONCLUSIONS: The use of hollow gold nanoparticles as carrier for betulin improved its in vitro antitumor efficacy thus offering an alternative therapeutic option.

Acknowledgment. This work was supported by UEFISCDI grant PN-III-P2-2.1-BG-2016-0354.

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P2F-3

Expression of miRNA-21 and -221 in clear cell renal cell carcinoma (ccRCC) and their possible role in the development of ccRCC

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BACKGROUND: Clear cell renal cell carcinoma (ccRCC) is the third most common urological cancer after prostate and bladder cancer but has the highest rate of mortality affecting over 40% of patients. microRNAs (miRNAs) are small non-coding RNAs that have become potential biomarkers and molecular targets for cancer treatment. Molecular markers such as miRNAs may have a role in the diagnosis of ccRCC.

AIM: In this study, we examined the expressions of miRNA-21 and miRNA-221 in renal cancer patients' tumor and adjacent paired normal tissues investigating the possible role of these miRNAs in the development of ccRCC.

RESULTS: Renal tumors (n=24) and paired normal renal tissue (n=24) samples, obtained from the Department of Urology, University of Debrecen, were analyzed for miRNA-21 and miRNA-221 expressions with qRT-PCR. miRNA-21 and miRNA-221 expressions were significantly upregulated in tumor specimens compared to normal tissue ($p<0.05$). miRNA-21 and miRNA-221 showed coexpression pattern in 19 (79.2%) cases of tumor samples and 8 (33.3%) cases of paired normal renal tissues. Increased miRNA pattern showed a positive correlation with pathologic TNM and Grade status.

CONCLUSIONS: Expression of oncogenic miRNA-21 and miRNA-221 in human ccRCC tumor tissue samples compared to adjacent nontumorous tissues might suggest that these miRNAs are involved in the development of ccRCC.

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P2F-4

Somatostatin receptors, as molecular targets in human uveal melanoma

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BACKGROUND: Uveal melanoma is the most common malignancy of the eye. Independently from the currently available treatments, half of the patients develop metastatic disease and survival of patients with metastasis is only 2-8 months. Previous studies demonstrated that various analogues of somatostatin can inhibit tumor growth. So far five subtypes of somatostatin receptors (SSTR1-5) have been identified, all of them are G-protein coupled receptors. Somatostatin and its synthetic analogues display the highest binding affinity to SSTR2 and SSTR5. In different human cancers and in cancerous vessels, the expression of SSTRs is higher than in normal tissues but their presence in human uveal melanoma has been investigated only in very limited number of samples.

AIMS: The aim of the present study was to investigate the mRNA expression of SSTRs in surgical specimens of 46 human uveal melanoma specimens and normal uvea tissue samples by RT-PCR. We also aimed to investigate the presence of SSTRs on two human experimental uveal melanoma cell lines, OCM-1, OCM-3.

RESULTS: According to our results, the majority of uveal melanomas expressed mRNA for SSTR2 (67,5%) and SSTR5 (66,6%). Among the normal uvea tissues, only one sample showed mRNA expression for SSTR2. Our results showed correlation with clinicopathological data.

CONCLUSIONS: Peptide hormone analogues represent an advantageous alternative for receptor based targeted therapy based on their relatively easy production, fast internalization and clearance, and suitable tumor penetration. Our results suggest that clinical use of subtype-specific SST analogues (i.e. *in vivo* scintigraphy, targeted therapy) might be beneficial in the treatment of human uveal melanomas positive for SSTR2 and/or SSTR5.

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P2F-5

The mechanism of action of targeted cytotoxic Luteinizing Hormone-Releasing Hormone analog AN-152 in doxorubicin resistant human uveal melanoma cells

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BACKGROUND: Cytotoxic analogs of LHRH can be successfully used for the treatment of hormone-dependent cancers (e.g.: prostate, ovarian, endometrial) but our knowledge on hormone-independent cancers such as human uveal melanoma (UM) is limited. Previously, we have demonstrated that 46% of UM express full-length LHRH receptors. This finding has led us to further examine the mechanism of action of LHRH receptor based targeted therapies in this malignacy.

AIMS: In the present study a doxorubicin-resistant human UM cell line ($OCM3_{DOX320}$) was established to investigate cellular uptake of doxorubicin and AN-152 on OCM3 and $OCM3_{DOX320}$ cell lines by confocal laser scanning microscopy. The LHRH receptor expression has been characterized by RT-PCR and immunocytochemistry.

RESULTS: Our results demonstrate the expression of LHRH receptor spice variants and isoforms in OCM3 UM cell line and its doxorubicin resistant form $OCM3_{DOX320.}$

It has been revealed by MTT assay that doxorubicin as well as AN-152 inhibited cell proliferation in a dose dependent manner in $OCM3_{DOX320}$ cells. Furthermore, receptor-mediated uptake of AN-152 was demonstrated using confocal laser scanning microscopy.

CONCLUSIONS: Our results suggest that the antiproliferative effect of AN-152 can be carried

even if only LHRH receptor isoforms are expressed. Our study also demonstrates the LHRH receptor mediated uptake of AN-152 in doxorubicin resistant $OCM3_{DOX320}$ cells. Our experiments provide new insights for the targeted therapy of UM and give further details about the accumulation of AN-152 in hormone-independent doxorubicin resistant cells expressing splice variants of the LHRH receptors.

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P2F-6

Concurrence of chromosome 3 and 4 aberrations in human uveal melanoma

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BACKGROUND: Although the incidence of uveal melanoma (UM) is low, it is the most common primary intraocular malignancy. Previously, we have demonstrated that approximately 50 % of UMs express type-I receptor for luteinizing hormone-releasing hormone (LH-RH-R). The gene encoding LH-RH-R is located in chromosome 4, however the occurrent numerical aberrations of chromosome 4 have never been studied in UM.

AIMS: In the present study we investigated the abnormalities of chromosome 3 and 4 and the possible correlation between them and also with LH-RH-R expression. 46 specimens of UM were obtained after enucleation. Numerical aberrations of chromosome 3 and 4 were studied by FISH.

RESULTS: Chromosome 4 could be detected in normal biparental disomy only in 14 (30 %) samples, however, 32 cases (70 %) showed more than 2 signals/nucleus. Monosomy of chromosome 3 could be found in 16 (35 %) samples. In 6 specimens (13 %), more than 2 copies of chromosome 3 were found, while normal biparental disomy could be detected in 24 (52 %) samples. Statistical analysis indicates significant ($p<0.05$) correlation between the copy number of chromosome 3 and 4. Moreover, moderate difference has been revealed in the survival rate of the UM patients with various pathological profiles.

CONCLUSIONS: Our results clearly demostrate abnormalities in chromosome 3 and 4 and the incidence of the monosomy of chromosome 3 in human UM. Our study provides new information about the genetic background of this tumor. These findings could contribute to a more precise determination of the prognosis of human uveal melanoma and to the development of new therapeutic approaches to this malignancy. Grant support: GINOP-2.3.2-15-2016- 00043 (G.H.), TAMOP-4.2.2/B-10/1-2010-0024 (E.S), the Gedeon Richter's Talentum Foundation (E.S.) and EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" project. .

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P2F-7

Antiproliferative evaluation of synthesized xanthene derivatives

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BACKGROUND: Xanthenes are important class of biologically active compounds due to their broad spectrum of pharmacological activities such as bactericidal, anti-inflammatory, antiviral and antiproliferative activity.

AIMS: The aim of study was to investigate antiproliferative activity of synthesized 2,2,5,5-tetramethyl-9-aryl-3,4,5,6,7,9-hexahydro-*1H*-xanthen-1,8(*2H*)-dione derivatives and the effect of substituent on investigated activity.

RESULTS: Five derivatives of 2,2,5,5-tetramethyl-9-aryl-3,4,5,6,7,9-hexahydro-*1H*-xanthen-1,8(*2H*)-dione were synthesized as potential antiproliferative agents. The *in vitro* antiproliferative activity of the synthesized compounds was investigated against a panel of tumor cell lines includ-

ing HeLa (cervical carcinoma), SW620 (colorectal adenocarcinoma, metastatic), HepG2 (human liver cancer), A549 (human lung cancer cell) and 3T3 (mouse embryo fibroblast cell line by using MTT colorimetric assay. Among synthesized compounds, 2,2,5,5-tetramethyl-9-(3′,4′-hydroxyphenyl) -3,4,5,6,7,9-hexahydro-*1H*-xanthen-1,8(*2H*)-dione (5) showed the highest antiproliferative activity against all tested cell lines. The most potent compound 5 were subjected to molecular docking simulations to preliminary find out the potential molecular target and at the same moment further support the experimental cytotoxic tests.

CONCLUSIONS: Structure-activity relationship studies revealed that substitution with two hydroxy groups on phenyl ring increase antiproliferative activity of xanthen-1,8 dione derivatives, while substitution with nitro or chloro group on aryl moiety do not affect on antiproliferative activity. Docking studies for the most potent compounds were carried out by taking amino terminal domain of topoisomerase II for anticancer activity against HeLa tumour cells. Docking study showed sites of importance in forming hydrogen bonds with receptors.

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P2F-8

The investigation of cancer stem cells in human uveal melanoma

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BACKGROUND: Uveal melanoma (UM) is the most common malignant tumor of the eye. In recent years, an exponentially growing number of studies have focused on identifying cancer stem cells (CSCs) in human melanomas[1]. If CSCs have a significant role in tumorigenesis, their frequency in primary tumors might correlate with tumor invasion, angiogenesis and metastasis- and in turn, with patient prognosis.

AIMS: Based on evidence for the existence of CSCs we investigated whether the expression of CSCs in UM is in correlation with survival or with the tissue subtype of the tumor or not. Clinical, pathologic and molecular data of 70 human uveal melanoma specimens were collected and the expression of CSCs were investigated in tissue samples. mRNA expression of CSC markers was studied in 18 UMs by RT-PCR and the protein expression of FZD6 CSC marker was evaluated in 52 UMs by IHC using tissue microarray (TMA) blocks.

RESULTS: The expression of Nestin, FZD6 and SOX10 CSC markers was detected in 100% of the UM samples. PROM1 and NGFR genes were expressed in 11.1% of the specimens. To extend the RT-PCR results, protein levels of FZD6 have been examined in 66 UM specimens with IHC-TMA technique. Kaplan-Meier curves showed no significant correlation (p=0.867) between the FZD6 expression and the survival of the patients.

CONCLUSIONS: CONCLUSIONS: The biological significance of stem cell markers, such as FZD6 in primary uveal melanomas remains unclear. Our results show a primitive neuroectodermal stem cell-like profile in a significant number of UM samples, which may indicate a higher risk for metastasis[2]. Further studies are needed to clarify the importance of stem cell marker sin human uveal melanoma. Grant support: GINOP-2.3.2-15- 2016-00043 (G.H.), the Gedeon Richter's Talentum Foundation (K.F.) and EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" project. .

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P2F-9

Investigation of the effect of cyclodextrin nanoparticles on MCF 7 breast cancer cell line by proteomics approaches

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BACKGROUND: Amphiphilic cyclodextrins (ACD), used in nanoscale as a drug delivery system, are molecules with the ability to spontaneously form nanoparticles. Paclitaxel loaded ACD have already been known as active against MCF 7 cells. There are also data available to show ACD have apoptotic effect on some cancer cell lines (1). However there is no information how the drug-free ACD have antiproliferative activity against MCF 7 cells on proteome level.

AIMS: This study aims to clarify the mechanism of anticancer activity of cyclodextrin nanoparticles on MCF 7 cells by proteomics studies.

RESULTS: Group T is MCF 7 treated with ACD, whereas C is not treated. T and C proteins in cytosolic fractions were separated by 2D gel electrophoresis. The spots having 1.5-fold change for T and C were analyzed by MALDI-TOF MS and identified by peptide mass fingerprint. Overexpressed proteins were hepatomaderived growth factor, heterogeneous nuclear ribonucleoprotein, and chromosomal protein homologue I. Underexpressed proteins with the influence of ACD were found as D-3-phosphoglycerate dehydrogenase (PHGDH) and keratin.

CONCLUSIONS: PHGDH inhibition has already been known to reduce tumor growth in breast cancers. In our study, 2.8-fold reduction in PHGDH compared to the C group is insightful to indicate the tumor suppressor properties of ACD against MCF 7 cell line.

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P2F-10

Investigation of anticancer action of a novel steroidal dimers of D-ring modified estrogens

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BACKGROUND: Estrogens are traditionally regarded as crucial factors of the reproductive systems, and it is well known that 17β-estradiol increases the proliferation of its target cells not only in the reproductive system but also in gynecological tumors. Our previous results show that D-ring modified estrogens including a triazol-substituted D-secoestone derivative have pronounced anticancer and antimigratory effects in different cell lines [1].

AIMS: Based on our previous D-secoestrone-triazol results, our aim was to investigate the antiproliferative effect of some newly synthetized and structurally related estrone dimer compounds.

RESULTS: The growth inhibitory effects of 8 newly synthesized D-secoestrone and 13-α-epiestrone linked dimer compounds were investigated by standard MTT assay on 9 different cell lines. Only one of them (DIM) has substantial antiproliferative action on all of the tested cell lines. The detailed investigation of the mechanism of action of DIM have been completed on three cerval carcinoma cell line with different HPV status (HPV 18-positive (HPV 18-positive HeLa, HPV 16-positive C33-A and HPV-negative SiHA cell lines). After 24 hours incubation the cells showed the morphological signs of apoptosis visualized by fluorescent double staining. After 48 hours cell cycle analysis exhibited significant increase in the number of cells in G2/M phase, followed by a G1 phase reduction, also elevation of the apoptotic subG1 population was observed regardless of the HPV status. The investigated DIM compound significantly enhanced the cell independent tubulin assembly in vitro. The cell migrating capacity was observed by wound healing assay.

CONCLUSIONS: These results suggest that one of our new estrogen dimer derivatives is a potent anticancer agent with proapoptotic effect proceeded by G2/M blockade, microtube stabilization and changes in cell motility.

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P2F-11

Investigation of anticancer properties of D-ring modified estrane analogs against a panel of breast cancer cell lines

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BACKGROUND: Estrane analogs without hormonal activities (e.g. those with modified in D-ring) have been recently proposed as basic structure for innovative antiproliferative and antimetastatic drug candidates.

AIMS: The aim of the present study was the investigation of the a set of 16-hydroxymethyl-estranes for their anticancer properties. The most potent agent was selected for additional in vitro investigation in order to describe the mechanism of the action as well as to test its action on the metastatic ability of cancer cells.

METHODS: Growth inhibiting effect of the estranes were determined by MTT assay using human breast cancer cell lines (MCF-7, T47D, MDA-MB-231 and MDA-MB-361). Fibroblasts were also used to determine the cancer selectivity. Cell cycle analysis was performed by flow cytometry. Wound healing assay and gelatin zymography were performed to evaluate the antimetastatic properties of the compounds.

RESULTS: Benzyloxy function and their p-substituted derivatives at position C-3 increased the antiproliferative potency. The most promising agents (IC50 values below 5 μM) exhibited a modest cancer selectivity. The selected molecules elicited a cell cycle disturbance with increased G1 and decreased S and G2/M population after 24 h incubation. The same compounds blocked the cell migration at subantiproliferative concentration and inhibited the activity of matrix metallopeptidase 9.

CONCLUSION: Estrane skeleton with modified D-ring can be regarded as a promising structure for design lead molecules with direct antiproliferative as well as antimetastatic capacity.

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P2F-12

In vitro antiproliferative properties of novel androstane-based synthetic steroids

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BACKGROUND: Antiproliferative properties of agents with steroidal backbone have been reported recently. Beyond their current therapeutic applications some 19-nortestosterone analogs with anticancer properties may be of high interest in early phase cancer research.

AIMS: The aim of our current work was the testing of a set of novel 19-nortestosterone analogs and their growth inhibiting activities on a panel of human gynecological cancer cell lines by means of MTT assay. The tumor selectivity of the promising analogues was determined by repeated assay on non-cancerous fibroblast cells. The most effective compound was selected for further experiments in order to describe the possible mechanism of action. Its direct cytotoxic effect was measured by LDH assay. The induction of apoptosis was evidenced by fluorescent microscopy and determination of caspase activities. The alterations in the cell cycle distribution were evidenced by flow cytometry. The influence on microtubule system elicited by the selected compound was determined using tubulin polimerization assay.

RESULTS: Three compounds (17α-chloro- (**1**), 17α-bromo- (**2**), 17α-iodo-19-nortestosterone (**3**)) showed substantial antiproliferative effect on HeLa cells (IC_{50}: 1.2–1.7 μM) with remarkable tumor selectivity (IC_{50} > 30 μM on fibroblast). The most potent analogue (**1**: IC_{50}: 1.2 μM) can cause moderate membrane damage and cell cycle blockade due to accumulation of the cells in S or G2/M phase. The increase of hypodiploid population (subG1) demonstrates the proapoptotic capacity of the agent. The induction of intrinsic pathway of programmed cell death has been proved by increasing activities of caspase-3 and -9 with unchanged caspase-8 activity. The selected compound exerted a direct action on tubulin dinamics by increase of the rate of polimerization in vitro.

CONCLUSIONS: According to our results the C17α substitution of the 19-nortestosterons with halogens is responsible for the antiproliferative effect. The most potent compound is capable of inducing apoptosis and has a temperate cytotoxic effect. This agent also causes a disturbance of cytoskeleton due to its influence on tubulin polimerization which may resposible for both of cell cycle arrest and the induction of apoptosis.

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P2F-13

Anticancer properties of sesquiterpene derivatives and their conjugates with estrogens on breast cancer cell lines

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BACKGROUND: Breast cancer is a leading cause of death in female population worldwide. The heterogenous aspects and different types of resistances necessiates the research of new drug candidates. Since most of currently applied agents are of natural origin their semisynthetic derivatives may have higher potencies.

AIMS: Our aim was to investigate the anticancer properties of newly prepared artemisinin derivatives and estrogen conjugates with no hormonal activities.

RESULTS: Antiproliferative effects of our original compounds, combinations of them and their new conjugates were determined by MTT-assay on four different breast cancer cell line (MDA-MB-231, MDA-MB-361, MCF7, T47D). Our investigations demonstrated that IC_{50} values of these new molecules were one order of magnitude lower than that of parent compounds which means a more potent antitumor effect. Morphological signs of apoptosis were detected after 24h incubation with our most potent conjugate on the most sensitive cell line (MDA-MB-361) by Hoechst-Propidium iodide fluorescent staining. Cell cycle analysis recorded by flow cytometry evidenced the increase of the ratio of MDA-MB-231 cells in G0/G1 phase followed by a decrease of the ratio of cells in S phase after 24h and 48h incubation indicating the inhibition of cell division.

CONCLUSIONS: This study provides experimental evidance that chemical conjugation of artemisinin derivatives and estrogens results in new molecules with more potent antiproliferative properties than their parent compounds. These new compounds can be considered as promising new candidates in the field of anticancer research.

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P2F-14

Searching for specific and clinically relevant BCRP (ABCG2) probe

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BACKGROUND**:** Breast Cancer Resistance Protein (BCRP/ABCG2) belongs to the G subfamily of the ATP Binding Casette (ABC) transporter proteins. BCRP localized at the apical membrane of epithelial cells of barrier tissues, handling a broad variety of endogenous and exogenous compounds. BCRP plays a role in drug absorption, disposition and excretion and regulates clinically relevant drug-drug interactions. Testing for BCRP is recommended by the regulatory agencies (FDA/EMA), although there is no widely accepted BCRP probe for the various *in vivo* and *in vitro* assays.

AIMS: To find a clinically relevant BCRP probe that is specific for BCRP, accepted by the regulatory agencies, applicable for various *in vivo* and *in vitro* assays, and commercially available.

RESULTS: Five candidates (chlorothiazide, rosuvastatin, sulfasalazine, teriflunomide and topotecan) were selected based on literature data and in-house experience. First, all five compounds were tested in vesiculare transport assay using BCRP, MDR1, MRP2, and MRP4 overexpressing Sf9 or Hi5 membranes. Four of these compounds

were then measured in vectorial transport assay on Caco-2 cells and BCRP overexpressing MDCKII cells. Chlorotiazide, sulfasalazine and teriflunomide were selective for BCRP in the vesicular transport experiments. In the monolayer system both chlorothiazide and teriflunomide were specific for BCRP.

CONCLUSIONS: Based on our results and literature data, chlorothiazide and teriflunomide meet all the required criteria for being a clinically relevant BCRP probe. However, further clinical data, for chlorothiazide in particular, are needed to establish these compounds as BCRP probes.

POSTER SECTION 2G PHARMACOLOGY

P2G-1

Antimicrobial and *in vitro* antiproliferative and proapoptotic potential against B164A5 murine melanoma cell line of flavonol fisetin

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BACKGROUND: Flavonoids represent one of the most studied classes of phytocompounds. Papers in the field show their role in the prevention of degenerative maladies including cancer, cardiovascular and neurodegenerative diseases [1]. Fisetin can be found in strawberries, apples, persimmons, mangoes, kiwi, peach, lotus root, onions, cucumbers and other fruits and vegetables. The flavonol was depicted for its anti-oxidant, anti-cancer, anti-angiogenic, anti-inflammatory, anti-diabetic neuroprotective and neurotrophic effects.

AIM: To analyse the antimicrobial and *in vitro* antiproliferative and pro apoptotic potential against B164A5 murine melanoma cell line of flavonol fisetin

RESULTS: Compared to standard antibiotics, the inhibition zones show that among the selected strains fisetin presents antibacterial activity against *E.faecalis, S. pyogenes, S.aureus, S.pneumoniae*. After 72 h of incubation and at a concentration of 100 μM, fisetin conduced to an average viability for B164A5 melanoma cells of 71,5 ±10,60 % respectively a percentage of 21,42±7,19 early apoptotic cells and 9,56±2,83 late apoptotic cells.

CONCLUSION: The flavonol fisetin can be reconsidered as a natural antibacterial agent against *E.faecalis, S. pyogenes, S.aureus* and *S.pneumoniae*. The anti-cancer activity against B164A5 cells is rather poor.

Acknowledgment: III-C5-PCFI-2017/2018-04 Roinextramam

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P2G-2

Antimicrobial and *in vitro* antiproliferative and proapoptotic potential against B164A5 murine melanoma cell line of flavonol quercetin

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BACKGROUND: Quercetin can be found in apples, grapes, red wine, blue and black berries, red cherries, citrus, green leafy vegetables, onions, cocoa, tea. Due to the plethora of biological activities it was described as a flavonol with multifaceted therapeutic applications [1]

AIM: To analyse the antimicrobial and *in vitro* antiproliferative and pro apoptotic potential against B164A5 murine melanoma cell line of flavonol quercetin

RESULTS: Compared to standard antibiotics, the inhibition zones show that among the selected strains quercetin presents antibacterial activity against *E.faecalis, S. pyogenes, S.aureus, S.pneumoniae*. After 72 h of incubation and at a concentration of 100 μM, quercetin conduced to an average viability for B164A5 melanoma cells of 51,2 ±14,14% respectively a percentage of 18,4±4,24 early apoptotic cells and 5,54 ±4,87 late apoptotic cells.

CONCLUSION: The flavonol quercetin can be reconsidered as a natural antibacterial agent against *E.faecalis, S. pyogenes, S.aureus* and *S.pneumoniae* and an antiproliferative agent against B164A5 melanoma cell line

Acknowledgment: III-C5-PCFI-2017/2018-04 Roinextramam

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P2G-3

Increased anterior cingulate cortex activation in migraine patients in response to acute citalopram administration

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BACKGROUND: In spite the high prevalence of migraine we do not know the exact pathomechanism yet. However, we know that specific abortive medications, triptans act through serotonergic system and serotonin neurotransmission is decreased in this condition. Neuroimaging studies also show functional and structural alterations of pain modulating brain areas in migraine. The anterior cingulate cortex (ACC) has important role in migraine by modulating top-down control of brainstem areas and receives dense serotonergic innervation from the raphe nucleus.

AIMS: In this study changes in ACC activation during and after 7.5 mg citalopram infusion, were measured in 27 healthy and 6 migraine volunteers using within-subject, placebo-controlled, double-blind, randomized design with challenge pharmacological fMRI (phMRI). The images were acquired at a 3T MRI scanner using T2*-weighted echo-planar pulse sequence with 3 mm x 3 mm x 3 mm resolution. The analysis was made with SPM12 in MATLAB by region of interest analysis of ACC.

RESULTS: We found significant differences in brain activation during and after citalopram challenge between migraine and control subjects in two clusters in the right ACC. The extracted time-series showed that the activation of ACC in migraine patients was significantly higher than in controls, especially in the first 8-9 minutes of drug administration.

CONCLUSIONS: Our findings clearly demonstrate that migraine patients are more sensitive to acute elevation of brain serotonin level, since they have increased ACC activation compared to the control group during and after citalopram challenge.

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P2G-4

The effect of acute escitalopram treatment on EEG gamma power during wakefulness and REM sleep

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BACKGROUND: Escitalopram, a widely used selective serotonin reuptake inhibitor (SSRI) antidepressant, is known to influence the sleep-wake cycle. Electroencephalography (EEG) enables to observe not only changes in the sleep architecture (e.g. time spent in different vigilance stages), but also alterations in different frequency bands which are related to specific brain functions. Gamma oscillations, at relatively high frequencies, play an important role in certain sensory and cognitive processes.

AIMS: We aimed to investigate whether acutely administered escitalopram caused EEG power changes concerning the slow gamma frequency band (30-60 Hz) in the relevant vigilance stages, wakefulness and rapid eye movement sleep (REMS). We used adult male Wistar rats equipped with electrodes, and registered EEG, electromyogram (EMG) and motor activity following intraperitoneal injections of 10 mg/kg escitalopram, starting at light onset.

RESULTS: Our results show that escitalopram altered gamma oscillations in the two examined vigilance stages in a different manner. During REMS, the SSRI caused a significant reduction in the gamma EEG power. In contrast, during wakefulness, escitalopram had no effect in this frequency range.

CONCLUSIONS: Since memory processes are important functions related to gamma activity during REMS, the decrease of gamma power in this stage may refer to memory loss as a result of the treatment. On the other hand, during wakefulness, gamma power remained unaffected, which implicates that brain functions connected to gamma band in this stage, such as attention and cognition, may not be affected by acute escitalopram administration.

P2G-5

Role of stress hormones in migraine

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BACKGROUND: Migraine is a disabling headache disorder which affects millions of people worldwide. Numerous factors can contribute to the development of migraine including stressors.

AIMS: Our aim was to review scientific knowledge about the relationship of migraine and stress.

RESULTS: Stress response controlled by the hypothalamo-pituitary-adrenocortical axis (HPA). Under stress corticotropine-releasing hormone (CRH) and aginine-vasopressine (AVP) are released from the hypothalamus and stimulates the secretion of adrenocorticotrop hormone (ACTH) from the pituitary gland. ACTH is the main hormone which leads to the production of cortisol. Migraine attacks are stressful stimuli and the brain of migraine patients could not habituate properly to these frequent stressors. As a result of impaired habituation, stress response termination compromised. Under normal circumstances cortisol binds to glucocorticoid receptors, which act as a negative feedback on the HPA. However, during chronic stress cortisol level remains continually elevated, which results in glucocorticoid receptor resistance and diminish the negative feedback control of CRH release. It leads to impaired anti-inflammatory processes and excessive glutamate release and eventually neuroplastic changes in the pain processing system.

CONCLUSIONS: The above mentioned processes, among others, play an important role in the development of chronic migraine. Therefore, understanding the interactions between chronic stress and pain processing may help in developing migraine preventive therapies.

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P2G-6

Cardiovascular effects of low- and high-dose beta-carotene treatment in Zucker obese rats

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BACKGROUND: Nowadays there is a growing interest in the components of plants as potential pharmaceutical raw materials. Among these beta-carotene is one of most intensively studied compound. Numerous clinical studies have examined the cardiovascular effects of it, but the results are quite contradictory. Beta-carotene could function as an antioxidant, however, many evidence show that it can act as pro-oxidant under increased oxidative circumstances 1.

AIMS: In the present study we investigated the cardiovascular effects of long-term, low and high dose beta-carotene treatment in hearts isolated from Zucker obese rats.

RESULTS: The glucose tolerance tests showed dose-independent reduction in blood glucose level. Furthermore, low dose treatment resulted in a significant increase in postischemic cardiac function, which was followed by decreased infarcted area. Moreover, high-dose beta-carotene treatment singnificantly increased the level of HO-1 in hearts subjected to ischemia/reperfusion. Interestingly, the observed cardioprotective effects are disappeared in case of high dose treatment, in spite of increased HO-1 level.

CONCLUSIONS: The observed controversial effects would be the result of formation of harmful oxidative products of beta-carotene during reperfusion.

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P2G-7

Effect of GSH synthetic analogue UPF1 on the activation of NRF2

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BACKGROUND: The synthetic analogue of GSH, a tetrapeptide UPF1 has recently developed by Ehrlich et al. which outperform free radical scavenging properties of GSH, while not showing any toxicity to the cells at 250 μM concentration [1]. We have previously observed that while UPF1 peptide itself is not capable of crossing the plasma membrane, the intracellular GSH concentration was increased when K562 cells were treated with 0.1 mM UPF1 peptide [2]. The expression of GSH is tightly regulated by the Nuclear factor (erythroid-derived 2)-like 2 transcription factor (NFE2L2) or simply Nrf2 which is released from its anchoring protein Keap-1and binds thereafter to the antioxidant response elements (ARE) during the oxidative stress.

AIMS: In the present study we investigated if the increase of the cellular GSH levels induced by the UPF1 peptide is related to the intracellular localization and expression of the ARE activating transcription factor NRF2.

RESULTS: We found that when HepG2 cells are incubated with 0.1 mM UPF1 peptide, the concentration of intracellular free Nrf2 increases already after 30 min. In K562 cells the Nrf2 concentration increases in the cytoplasm after 45 min incubation. At the same time, Nrf2 concentrations in the nucleus are at the minimum in both cell lines after 30 min incubation with the peptide.

CONCLUSIONS: The results suggest that UPF1 peptide activates the intracellular antioxidant defence system and while the initial step of this activation remains to be determined, the key step in the process is the activation of Nrf2.

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P2G-8

Vasoactive effects of a new nitric oxide donating acetylsalicylic derivative

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BACKGROUND: According to the latest WHO mortality rates ischemic heart conditions are the main cause of death among non-communicable diseases.

AIMS: In the following investigation we have aimed to test the properties of a nitric oxide (NO) donating acetylsalicylic acid (ASA) derivative, which is stable, water soluble compound newly synthetized at the University of Debrecen, Hungary.

RESULTS: In the first part of our experiments we were tested the possible cytotoxic effects of our ASA derivative *in vitro* in 10^{-4} – 10^{-7}M concentrations. MTT cell viability assay and hemolysis tests were performed on H9c2 cells and rat erythrocytes, respectively. Thereafter, we were measured the vasoactive effects on female Sprague Dawley rats *ex vivo* according to the Langendorff method in the presence or absence of the NO donating molecule. Our new NO donating ASA derivative is not affecting negatively to the cell viability in the tested concentrations. Furthermore, we have noticed a dose-dependent, out washable vasodilation on coronaries.

CONCLUSIONS: Based on the beneficial observations through our experimental arrangement, the new molecule synthetized in our University is a powerful vasodilator with no significant toxic effects. It may contribute to new therapeutic approaches against ischemic heart diseases and possibly related syndromes, but the molecular mechanisms needs to be clarified.

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P2G-9

The study of the fenugreek seed treatment and its effects on certain methabolic parameters and on the mithocondrial functions

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BACKGROUND: The *Trigonella foenum-graecum*, fenugreek is a medicinal plant used since ancient times, it is also listed in the Pharmacopoeia. It contains numerous biologically active compounds. The fenugreek has a great impact on the metabolism of lipids and glucose, insulin-sensitising, has antioxidant effects, it contributes in keeping the energy balance. Mithocondrial enzymes, like citocrom c or sirtuins, have an important role in this. The citocrom c enzymes also take part in oxidative processes and by being released from the mithocondria they can start the programmed apoptosis. Sirtuins are NAD+-dependent proteins, regulates several cellular processes like aging, transcription, apoptosis, inflammation, stress resistance, energy balance, insulin sensitizing, circadian clocks and mitochondrial biogenesis.

AIMS: We conducted a chronic feeding study on rats. The goal of our study is to analyse the effects of the fenugreek seed (0,6 g/kg) on metabolic parameters (nutrients and water consumption, weight), on glucose metabolism and on mithocondrial energy production.

RESULTS: The studied rats showed a significant increase in body weight after four days opposed to the control group, the same increase could also be observed in their lipid accumulation, this difference was present until the end of the treatment. We have found no difference in the insulin's effectiveness and neither did the insulin sensitivity change. While studying the integrity of the external mithocondrial membrane, no signifficant differences were found between Control (47,56± 1,668) and Treated (47,33± 1,863) groups. Measuring the enzyme activity no signifficant differences were found between Treated (88,18± 1,798) and Control (88,82± 2,110) groups either.

CONCLUSIONS: All things considered, we can say that the treatment strengthened the weight increasing effects of chronic feeding with lipids and glucose. Although the calorie consumption of the two groups was the same, the body's lipid content has increased in the treated group. The integrity of the external mithocondrial membrane has not changed. The sirtuin activity has increased, however, the causes of this mechanism are not completely clarified yet.

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P2G-10

The cardioprotective effect of metformin on doxorubicin-induced cardiotoxicity

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Doxorubicin (DOX) is one of the most effective chemotherapeutic agent, but its cardiotoxicity has been an important clinical limitation. However, molecular mechanisms underlying DOX cardiotoxicity are still being uncovered, but known to involve, at least in part, mitochondrial dysfunction, oxidative stress and apoptosis. In recent years, a number of studies have investigated the role of autophagy on DOX-induced cardiotoxicity but to date it is not clear how DOX alters that process and its consequence on cardiomyocytes.

The aim of our study was to investigate the possible protective role of the antidiabetic drug metformin (MET) and its effect on autophagy in a model of DOX-induced cardiotoxicity. Sprague-Dawley rats were randomly divided four group. The DOX group rats received doxorubicin (3 mg/kg every second day, cumulative dose: 18 mg/kg) intraperitoneally. The MET group rats received metformin (250 mg/kg/day for two weeks) via gavage. The DOX+MET group rats received doxorubicin + metformin at the same dose. Control group rats received distilled water and saline. After the last dose of doxorubicin isolated working hearts were prepared and heart function parameters (aorta flow, heart rate, coronaria flow and aorta pressure) were evaluated. Serum level of LDH, CK-MB enzymes, Troponin-T, and cardiac MDA were measured. Heart tissue samples were histopathologically examined. Western blot analysis was conducted for autophagy-associated proteins P62, LC3, beclin-1, mTOR and AMPK.

Results of our study revealed that treatment with metformin produced increased cardiac protection manifested by a significant decrease in serum Troponin-T and cardiac MDA level, and remarkable improvement in the heart function and in the histopathological features. Furthermore, by focusing on the contribution of LC3, P62, beclin-1, mTOR and AMPK pathways, we have found that metformin induced autophagy and increased the expression of AMPK which may help cardiomiocytes to survive during doxorubicin treatment. These results may suggest using metformin would be preferable drug for patients suffering from cancer and receiving DOX in their chemotherapy regimen.

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P2G-11

Investigation of the effects of anthocyanins on human inflammatory keratinocyte model

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BACKGROUND: Psoriasis is a chronic inflammatory skin disease in which IL-17 and TNF-α play an important role in its pathology. Anti-cytokine therapies are the most effective methods nowadays, nevertheless natural products render adjuvant treatment opportunities in psoriasis.

AIMS: Keratinocytes are widely used for inflammatory modelling of psoriasis. In our recent study we investigated the role of TNF-α and IL-17 in inflammation and proliferation on human keratinocyte (HaCaT) cell culture models. Our aim was to establish a sensitive psoriasis model to reveal the anti-inflammatory and anti-proliferative effect of anthocyanins.

RESULTS: The NF-κB immunostaining results show the role of cytokines in inflammation in the applied concentration. Anthocyanins efficiently blocked the activation of NF-κB pathway. We detected different proliferative effects of stimulants on real time cell analysis (RTCA) and confirmed the anti-proliferative effect of anthocyanins. Proinflammatory cytokines affected cell proliferation in different extent; however anthocyanin pre-treatment decreased the proliferation rate on cytokine stimulated HaCaT cells in wound healing assay.

CONCLUSIONS: The results indicate that anthocyanins could affect and inhibit the proliferation and inflammation on inflammatory HaCaT cell model.

This work was supported by EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" project.

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P2G-12

Iron (II) chelator could prevent the loss of positive cardiovascular effects of high dose beta carotene treatment

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Background: Beta carotene (BC) is a good antioxidant compound, however, there are increasing evidences suggesting the prooxidant effects of it under heavy oxidative stress. Earlier we studied the effects of it under ISA/REP-induced increased oxidative circumstances. In that study we found that the cardioprotective effects of BC are lost after ISA/REP when the agent was administered at high concentration. Although, BC treatment increased HO-1 expression, we did not observe a better heart function and/or decreased IS in case of high dose treatment. (1). HO-1 is an enzyme produced in response to oxidative stressors and may contribute to loss of cardioprotection at elavated BC dosage. Fe^{2+} produced under normal HO-1 activity is a harmless metabolite and clears up spontaneously. As Fe^{2+} boosts the prooxidant characteristics of high dose BC, it possibly undermines the cytoprotective effects of HO-1 and increase oxidative stress on a tissue. We hypothesize using a selective chelator of Fe^{2+}, desferal, may negate the loss of cardioprotection at high dose of BC.

Aims: In the present study we investigated if desferal, can prevent the loss of positive cardiovascular effects in high dose BC treatment in isolated rat hearts. Adult male rats were gavage-fed BC for 4 weeks, at dosage of 150mg/kg/day. The hearts were then excised from the animals and mounted in a working heart apparatus and subjected to 30 min of global ischemia, followed by 120 min of reperfusion. The cardiac functions were evaluated and infarct size were assessed.

Results: We observed that desferal increases postischemic cardiovascular function alone or in combination with high dose beta carotene treatment. Furthermore, the iron (II) chelator improved the cardiovascular recovery which is reflected in reduced infarct size.

Conclusion: Iron (II) chelators can possibly prevent the loss of positive cardiovascular effects in case of high dose BC treatment.

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P2G-13

Characterization of D-serine transport in SH-SY5Y cell line and cortical astrocytes

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BACKGROUND: D-serine is a co-agonist of the NMDA-glutamate receptors. Hypofunction of NMDA receptors has been connected to several CNS diseases, e.g. schizophrenia and bipolar disorder. Decreased extracellular level of D-serine may contribute to their pathophysiology. Various transport systems, like sodium dependent ASCT1 and 2, as well as sodium-independent asc1 were reported to be involved in D-serine uptake [1]. These transporters are potential targets for modulation of intra- and extracellular D-serine level.

AIMS: Characterization and comparison of D-serine uptake into SH-SY5Y human neuroblastoma cell line and rat primary cortical astrocytes.

RESULTS: Time- and dose dependent D-serine uptake was observed in both cell types. Main transport form was found sodium-dependent since about 80% less D-serine uptake was measured in a sodium-free buffer. Neutral amino acids, substrates of these transporters, e.g. L-alanine and L-threonine concentration dependently inhibited D-serine uptake, characterized by a two-step inhibition curve and complete inhibition at their highest concentration in both cell types. According to literature data ASCT1 can be selectively inhibited by trans-4-hydroxy-L-proline (t-proline), while L-glutamine was reported as a preferential inhibitor of ASCT2 [1]. In the studied concentration range t-proline reached only about 55% inhibition of D-serine uptake in both types of cells. In the first, selective step the inhibition was about 25%, possibly indicating the contribution of ASCT1 to D-serine uptake. L-Glutamine provided more pronounced inhibition in two steps in SH-SY5Y cells and astrocytes alike. The first step, supposedly related to ASCT2 was responsible for about 60% of D-serine uptake.

CONCLUSIONS: Both primary astrocytes and SH-SY5Y cell line show mainly sodium-dependent D-serine uptake with at least two transporter systems involved. Further characterization of these transporters is needed. SH-SY5Y cells are likely to be appropriate for studying the opportunities of D-serine transporter modulation.

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P2G-14

Comparison of the cytoprotective effect of some resveratrol derivatives

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BACKGROUND: Previously we have found resveratrol shows strong protective effect against serum deprivation induced caspase activation in non-transformed fibroblasts. According to our recent results the role of mild intracellular stress that activates stress resistance machineries plays a crucial role in the protective effect (1).

AIMS: In the present study we aimed at examining structure activity relationship by using resveratrol derivatives.

RESULTS: Apoptosis was induced by serum deprivation in primary mouse embryonic fibroblasts. Caspase 3 activation was assayed by using its fluorogenic substrate. Reactive oxygen species production and depolarization of the mitochondrial membrane were measured by fluorescence methods. The effect of oxyresveratrol, pinostilbene, pterostilbene, trimethyl resveratrol was compared to that of resveratrol.

We found that oxyresveratrol and pinostilbene (monomethyl resveratrol) with very similar chemical structure to resveratrol exerts a resveratrol-like protective effect. However; pterostilbene, (dimethyl resveratrol) was found to have strong cytotoxic property thus cannot be further analyzed. Trimethyl resveratrol also significantly reduced caspase 3 activation although its effect was much less

pronounced. This latter compound caused much more considerable depolarization of mitochondria and consequential free radical generation than resveratrol and its protective derivatives did.

CONCLUSIONS: Oxyresveratrol and mono- and trimethyl resveratrol posses resveratrol like protective effect, while the dimethyl derivative has strong cytotoxic activity. The reduced efficacy of trimethylated derivative raises the possibility of importance of presence of antioxidant phenolic hydroxyl groups in the protective effect.

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P2G-15

In vivo hypoglycemic activities of ethanol and aqueous extracts of *Capparis ovata* var. *Palaestina*

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BACKGROUND: Diabetes mellitus (DM) is a global public health problem with expected 300 million diabetics by the year 2030 worldwide. There is a need to search for safe, more affordable and widely available or easy to produce medication for treatment of DM. Therefore investigating the efficacy of plants could be a better alternative. *Capparis ovata* var. *palaestina* has wide natural distribution in Turkey (1,2).

AIMS: The aim of this study is to evaluate hypoglycemic effect of *C. ovata* var. *palaestina* extracts in alloxan induced diabetic mice. For this purpose bud and fruit extracts of *C. ovata* var. *palaestina* were prepared. Glibenclamide and saline was used as control.

RESULTS: Diabetic mice were administered with 100, 300, 500 mg/kg (i.p.) doses of bud and fruit's ethanol and aqueous extracts. Fasting blood glucose levels were screened 60, 120, 240 and 360 min after treatments. Statistical analysis results was performed using one-way ANOVA followed by Dunnett's post-tests. The administration of the glibenclamide (3mg/kg,GC) significantly decreased blood glucose at 60 min ($p<0.01$), 120 min ($p<0.01$), 240 min ($p<0.001$) and 360 min ($p<0.001$) when compared with diabetic control (DC). The administration of the fruit-aqueous (FA) extracts; FA1 (100mg/kg) at 60 min ($p<0.05$), 120 min ($p<0.05$) and FA2 (300mg/kg) at 60 min ($p<0.01$), 120 min ($p<0.01$), 240 min ($p<0.05$) and 360 min ($p<0.05$), significantly decreased blood glucose level when compared with DC. On the other hand administration of the bud-aqueous (BA) extracts; BA3 (500mg/kg) at 60 min ($p<0.001$), 120 min ($p<0.01$), 240 min ($p<0.001$) and 360 min ($p<0.001$), significantly decreased blood glucose level when compared with DC. None of ethanol extracts did not show any significant changing on blood glucose level.

CONCLUSIONS: The results of this study showed that the aqueous extract of C. ovata var. palaestina may have potential hypoglycemic activity.

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POSTER SECTION 2H
HOSPITAL PHARMACY AND PHARMACOEPIDEMIOLOGY

P2H-1

Bisphosphonate related osteonecrosis of the jaw in Hungary

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BACKGROUND: Bisphosphonate (BP) related osteonecrosis of the jaw (BRONJ) is a serious side effect of the bisphosphonate group. As this disease has no independent code in The International Statistical Classification of Diseases and Related Health Problems (ICD), it is hard to estimate how many bisphosphonate patients are affected.

AIMS: The aim of our study was to find epidemiology data of Hungarian BRONJ patients. We also mapped the risk factors of BRONJ: main diagnosis of the BP treatment as well as medication administered besides bisphosphonate, and socioeconomic factors.

RESULTS: In our study we defined BRONJ patients treated from 2010 to 2014 with the help of

ICD codes and the International Classification of Procedures in Medicine (ICPM) from the database of the National Health Insurance Fund of Hungary. We identified the basic disease treated with bisphosphonate, whether it was malignancy or non-malignant disease. 236,207 bisphosphonate patients' socioeconomic and medication data were analyzed, out of whom 340 developed BRONJ according to our definition. Although more women developed BRONJ in our patient population, we found significantly more men in the necrosis group than in the total patients' group. We found that oncology patients are at the highest risk of developing BRONJ, especially if BP is administered intravenously. Therapy change has no proven effect on the number of our patients developing BRONJ. Steroids and chemotherapy increase the risk of BRONJ, and we also found differences between the BP groups.

CONCLUSIONS: In the group of bisphosphonate patients, oncology patients, intravenously administered BP patients, and patients taking steroids are at a higher risk of developing BRONJ. Differences between our results and the international data highlight the effect of patient related other factors on the development of BRONJ. Our findings confirm that bisphosphonate patients need closer monitoring due to this serious side effect.

P2H-2

Cross-Cultural adaptation of the "Osteoarthritis Knee and Hip Quality of Life" disease specific questionnaire – methods and results of the Pilot phase I.

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BACKGROUND: Osteoarthritis (OA) is highlighted disorder with important socio-economic factors affecting the patient adherence and patients' quality of life. WHO report handles this as one of the most important chronic disease. OA is counted as the leading cause of chronic disability and permanent loss of quality of life. There is an urgent need to focus on the main factors affecting the disease state, and also to have an overview on the status of the Hungarian population. Lower limb osteoarthritis specific quality of life questionnaire is not available in Hungary.

AIMS: The aim of this work was to develop the cross-cultural adaptation of the „Osteoarthritis Knee and Hip Quality of Life" questionnaire for the Hungarian population according to the relevant international guidelines and instructions of the French questionnaire development team.

RESULTS: Hungarian cross-cultural questionnaire was developed according to the adaptation and validation guidelines. The Pilot I. study was performed at The Rehabilitation Center in Kiskunfélegyháza; 34 questionnaires were evaluated of the filled 40. 70,58% of the sample was women, the mean age was 72,5. The education level in most cases was primary school and 44,12% lived at the village area. Only one from the 43 items of the questionnaire was ignored, this was in connection with sexual activity of the patients (an item required to vacate, if more then 5% of the fillers do not answer it).

CONCLUSIONS: This study completed the Pilot I. part of the national implementation of the international questionnaire, measuring the quality of life in case of OA patients in Hungary. The questionnaire measures the Hungarian arthritic population in four domains: physical activities, mental health, social functioning, and social support. The next step is a further pilot to evaluate reproducibility and construct validity.

The work was supported by Foundation for Development of Pharmacy Education at University of Szeged.

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P2H-3

Screening potential interactions between drugs and supplementary products: Summarized experiences and recommendations based on the study of three Hungarian patient groups

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BACKGROUND: The increasing number of patients taking supplementary products (OTC medicines, herbal remedies, dietary supplements, etc.) along with prescribed medicines has become a new challenge for health care systems. These products may influence therapy outcomes by inducing unwanted effects.

AIMS: Our aim is to summarize the results and practical observations from our previous studies.

RESULTS: We studied the use of supplementary products with three different patient groups (patients of internal medicine – n=200, psychiatry – n=54, Parkinson's disease – n=26). Potential drug-drug and drug-supplement interactions were identified and analyzed. The ratio of supplement users varied between 46-91%. However, the prevalence of clinically relevant and potentially serious interactions may be about one order of magnitude less. The general risk of harmful interactions is hard to estimate because of the contradictions between the interaction databases, the numerous factors influencing the clinical relevance and the significant differences observed between the patient groups. Participants had different attitudes regarding supplements and prescribed medicines. The most common reason for taking supplements was that patients wanted to play an active role in their own recovery.

CONCLUSIONS: Although computerized interaction screening can be of great help, current databases show great variability and have several limitations. Lack of a comprehensive and verified database that includes all supplementary products and the lack of a generally accepted nomenclature of ingredients make the recognition and prevention of drug-supplement interactions more complicated. Standardized and transparent classification of risk and clinical significance of interactions can only be established through structured assessment of underlying evidence.

P2H-4

Alarming patient safety concerns of the illegitimate online market of shortage oncology drugs

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BACKGROUND: Shortages of oncology drugs mean a challenge to healthcare systems. Exposed patients or health care providers may seek alternative resources online. Unfortunately, consumers may be misled by unreliable information resources and the enormous number of illegitimate online medication vendors. Illegally distributed medications may negatively influence the success of therapies, furthermore counterfeit medicines pose potential health hazard.

AIMS: The purpose of our study was to evaluate the online accessibility of oncology drugs affected by drug shortages at national and at international level in the past years. Patient- and medication safety issues were identified to highlight the dangers of the unregulated sale of possibly life threatening products

RESULTS: Shortage oncology drugs are generally available on the Internet and are accessible without medical prescription by majority (73.4-78.4%) of the identified (n=210) websites. Numerous (20.3%-26.9%) vendors do not display any contact information on their websites and in most cases (90.5%- 87.3%) no healthcare professional is available for customers. None of the evaluated websites were approved/recommended by Internet pharmacy verification databases, while 31.1% were definitely unregulated. Numerous Internet vendor sites (63,5%) operated in both evaluated years, indicating illegitimate sellers' continuous service.

CONCLUSIONS: The alarming illegitimate market of shortage oncology drugs has been identified. The limited access to pharmaceuticals within the traditional supply-chain is a challenge for healthcare but an opportunity for fraudulent online sellers of medications. Managing illegal trade of pharmaceuticals and limiting access to potentially counterfeit drugs must be a priority for governments and drug supply systems. Future goals of the authors: identification of the online availability of further active ingredients used in oncology treatments, evaluation of the quality of therapy related information provided by online medication sellers.

P2H-5

The effect of clinical pharmacy services on medication errors in a Hungarian regional hospital

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BACKGROUND: Medication errors are a significant and costly cause of injury during hospitalization that can effectively be mitigated by clinical pharmacist interventions. In October 2016, clinical pharmacy services were introduced in 4 departments of the „Szent Borbála" Hospital in order to facilitate patient safety and minimize medication errors.

AIMS: To assess medication errors on 4 wards for an 8-month period and to investigate the potential outcomes of implementing clinical pharmacy services in those settings.

RESULTS: Since October 2016, 2189 patients were screened on 4 wards. Errors identified during the medication reconciliation and review processes were classified according to the Pharmaceutical Care Network v7.0 scheme. Pharmacist interventions and their acceptance rate were also recorded. Medication error rates differed substantially between medical specialties. The long-term care ward showed a markedly high, 32% error rate, while wards of internal medicine demonstrated a moderate 6-8% rate and the department of surgery exhibited the lowest value at 5%. The most frequent errors were drug interactions (25%), followed by inappropriately high doses (13%), duplications (10%) and contra-indicated drug combinations (6%). The overall acceptance rate of pharmacist interventions was 80%. Non-acceptance due to risk/benefit assessments occurred in 11% of the cases, while no reason of refusal was provided in the remaining 9%. Reconciled medication errors of surgery patients were also referred to their primary care physicians.

CONCLUSIONS: It was found that the implementation of clinical pharmacy services is a useful and effective method of enhancing patient safety. Medication reconciliation and review has the capacity to identify and resolve issues of the prescribing, dispensing and medication use processes. Direct involvement of pharmacists in the clinical setting has also facilitated a highly functional, result-driven and multiprofessional approach of patient care.

P2H-6

Assessment of some herbal products used to treat urinary tract diseases in Hungary

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BACKGROUND: Due to the increased demand for herbal remedies, the number of products and distributors is also increasing worldwide. The quality, safety, and efficacy of these products is not as well-regulated as in the case of medicines, however, the patients are not aware of this difference.

AIMS: Because of popularity of herbal products in self-treatment of urinary tract infections in Hungary, we prepared questionnaires for both laypersons and professionals (pharmacists and pharmacy technicians) to assess their general judgement on them. Then according to the recommendations of the Ph. Eur. (1) and another protocol (2), we investigated some herbal products containing Solidaginis herba, Uvae ursi folium, Equiseti herba, and Vaccinium macrocarpon fructus.

RESULTS: Half of the laypersons (127 persons) answered, that they first seek medical help in the case of urinary tract symptoms, about 30% (81 persons) preferred self-medication with the help of the internet, and only 14% (37 persons) asked the help of a pharmacist. According to the TLC chromatograms, all products contained the marker compounds of the medicinal plants, but the HPLC and spectrophotometric methods revealed considerable quantitative differences between them. All products of Equiseti herba were of pharmacopoeial quality, but the arbutin, flavonoid, and proanthocyanidin content of preparations containing Uvae ursi folium, Solidaginis herba, and Vaccinium macrocarpon fructus, respectively, met the standards only in few cases

CONCLUSIONS: All examined distributors had products with both better and worse quality, and we could not find any correlation between the quality of the products and the popularity of the distributors among both laypersons and professionals.

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P2H-7

Results of a pharmacist led medication reconciliation process

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BACKGROUND: Medication discrepancies are common. Studies suggest that they occur in up to 70% of patients at admission or discharge. Medication reconciliation is a strategy to reduce the occurrence of medication discrepancies that may lead to adverse drug events.

AIMS: A medication reconciliation process was introduced in three wards of our hospital in order

to improve drug therapy and patient safety. Medication histories are taken by a clinical pharmacist or pharmacy assistant. Patient data, medication list according to drug chart and notes of medication anamnesis are recorded on a form, discrepancies and requests for intervention can be highlighted. In addition, the form includes risk categorization based on general criteria (eg. polypharmacy) and fields for drug allergies, side effects and high alert medications. The data of 114 forms from two wards (Septic and General Surgery) were collated and analysed in Microsoft Excel.

RESULTS: 99 patients (87%) were considered as "at risk". The most common risk categories were polypharmacy (90 cases) and high alert medications (72 cases). The average number of medications taken by a patient was 8. In 72 cases (63%) there was at least one discrepancy between the drug chart and the medication history. The two most common types of discrepancy were patients taking medications that were not recorded on their charts (36 cases) and missing or inappropriate doses (27 cases), accordingly these were the most frequent interventions too. The total number of interventions requested was 177. 72 patients were monitored further during their stay and 42 had a consultation at discharge.

CONCLUSIONS: Medication reconcilliation plays an important role in reducing potential drug related problems. The collation and analysis of data highlights areas for improvement. There would be benefits in further extending the process beyond admissions to discharge and other critical handover points in the patient care pathway.

P2H-8

Polypharmacy among hospitalized elderly patients

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BACKGROUND: Polypharmacy (taking 5 or more chronic medications concomitantly) is a common problem among elderly patients. Concomitant use of many drugs may increase the presence of drug-related problems and decrease the quality of life and compliance. Besides this, several medications are potentially inappropriate for elderly patients and these medications should be avoided or changed.

AIMS: The aim of the study was to review and evaluate the medication of elderly, hospitalized patients and to assess the prevalence of polypharmacy and potentially inappropriate medications (PIM). The collection of data was carried out between the period of Janurary 2011 and December 2012, patients 65 years old or above were recruited from the Traumatology Department. Data were recorded from the patients' charts and documentation and a retrospective analysis was performed.

RESULTS: 604 patients met the inclusion criteria (143 male, 461 female; mean age: 81.8±7.52). On admission, the mean number of chronic medication was 7.1±3.8. The prevalence of polypharmacy was 74.0% (75.3 % among female patients and 69.9% among male patients). 26.2% of the patients were taking 10 or more medications concomitantly. Regarding ATC codes, the most prevalent anatomical main groups were group C (85.3% of patients), group N (72.9%) and group A (68.9%). The most frequently used active agents were acetylsalicylic acid (30.8% of patients), amlodipine (30.5%), piracetam (28.6%), alprazolam (27.2%) and pantoprazole (27.15%). Two of these agents-piracetam and alprazolam- are considered as PIM medications. Regarding PIM medications, 76.8% of patients were taking at least one PIM.

CONCLUSIONS: Although polypharmacy is a common problem among the elderly and comorbidities demand the concomitant use of several medications, this group requires special attention. To avoid possible drug related problems, regular medication review, simplification of treatment, avoiding or changeing PIM medications and patient education is necessary.

P2H-9

Importance of pharmaceutical care in the application of eye drops and determination of microbiological contamination

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BACKGROUND: It is considered to be a huge risk

factor of infectious eye diseases when the patient uses contaminated eye drops due to inadequate adherence.

AIMS: Our aim was to investigate the effect of magistral preparation conditions of different eye drops dispensed in hungarian community pharmacies, including also the patient adherence and its effect in the change of microbiological stability using preparation and eye drop administration models.

RESULTS: According to the results of microbiological investigations there was no initial aerob contamination detected rigth after the preparation of eye drops – applying three different methods. However there was a significant risk for the contamination applying increased airflow and non-aseptic conditions. The applied eye drop administration model resulted revelation of contaminant microbes in the preparation.

CONCLUSIONS: Preparation conditions of magistral eye drops is well-defined and can assure the proper microbiological cleanliness. Instruction provided for the patient in collaboration with ophthalmologists on the application of eye drops should be an integral part of pharmaceutical care. In conclusion the microbiological stability of eye drops is depending on both the preparation method – including the right choice of the preservative agent and the adequate administration.

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P2H-10

Physical compatibility of vancomycin with common continuous administered drugs in the intensive care unit

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BACKGROUND: For the better pharmakokinetic/pharmakodinamic and less toxic effect, vancomycin is often used as once daily dosing (2g/24 h) regimen as continous infusion in the intensive care unit. During the co-administration of intravenous drugs via Y-site, in line incompatibility may occur.

AIMS: Our goal was to detect the possible incompatibility of vancomycin and other continuously administered drugs. Simulated Y-site administration was accomplished by mixing vancomycin and crystalloids, opioid analgesics (morphin, fentanyl, sufentanyl), cardiovascular drugs (urapidil, clonidin, nitroglycerin, amiodaron), heparin and regular insulin in a 1:1 (v/v%) ratio in polypropylene syringe. The aliquot samples were evaluated by visual observation, pH measurment and microscope immediately (t0) and 60 (t60) minutes after preparation.

RESULTS: A total of 13 drug pairs were investigated. Vancomycin was proven physically incompatible with heparin and one of the crystalloids (white precipitation occured immediately after mixing). The pH ranges of the other 11 samples were 3.21 – 4.85 after mixing. This pH ranges were acceptable based on the physical properties of each drugs. The pH measured at t60 and the highest change was only 0,10. During the microscopic examination we found microparticules at t0 (min.-max.:20-70 um) and also at t60 (min.-max.:8.7-24.4 um).

CONCLUSIONS: Eleven of the total 13 drug pairs are considered physically compatible therefore co-administration through Y-site are considered safe.

P2H-11

Impact of clinical pharmacy services in a multidisciplinary intensive care unit

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BACKGROUND: Providing adequate therapeutic management for critical care patients is crucial in decreasing the incidence of complications during hospitalisation by enhancing medication safety, nutritional status and supporting the healing process.

AIMS: To describe the activities of clinical pharmacists in the Intensive Care Unit (ICU) of the Péterfy Hospital and Trauma Center, including pharmacist-led therapeutic monitoring of perioperative and septic patients

RESULTS: The following clinical pharmacist activities were put in practice: providing drug information for physicians and nurses; clarification of drug orders; drug accessibility information; pharmacokinetic consultation; detection and re-

porting of adverse drug reactions; therapeutic consultation leading to changes in drug therapy and assessment of patient nutritional status and general ICU-specific parameters (vasopressor need, length of stay, length of mechanical ventilation, beginning of mobilization, mortality). These activities, as well as a thorough knowledge of patients' issues serve to identify pharmacotherapy problems and to facilitate interventions that address potential errors, often before an incorrect or suboptimal therapeutic measure is taken.

CONCLUSIONS: Dedicated critical care pharmacists can play a useful and effective role in a multidisciplinary ICU healthcare team. While pharmacist can identify and prevent errors, it remains difficult to assess the impact of what has otherwise been prevented. This seems to be an inherent problem of the ICU setting, where advanced monitoring techniques combined with a highly skilled multiprofessional team allow identification of certain trends before they become clinically significant issues. Importantly, pharmacists providing comprehensive medication management do enhance the teams' ability to recognize and address these issues in time. They also provide continuity in individualized care and high-level coordination in collaborative practice to improve patient safety and therapeutic outcomes.

P2H-12

Impact of patient education programs among adolescents

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BACKGROUND: Today, the side effects are responsible for the 5th common cause of death in the USA and EU. This also means 80 billion euros/year additional cost for health economics. The development of side effects can be a consequence of interactions, but also can happen because of incorrect medication.

AIMS: At the age of 14, people are allowed to buy their own medicines, but it is questionable if they understand the informative leaflet. Our aim was to evaluate their health status and their level of knowledge about the safe use of medications; the impact of demand within the framework of the national educational system of health-education and wheter the pharmaceutical care provided by pharmacists can be possibly in support for this age.

RESULTS: Meanwhile, the self classified health status of respondents were 4.03/5.00; 24% of them take regular medication. 84% of students were ever used drugs as a purpose of self-medication, 21% never goes in a pharmacy, 45% never heard about pharmaceutical care. If they have questions about their health and medications, most of the respondents turn to their parents. They use websites to search information while only 14% found the internet trustworthy. Based on our results, we prepared a presentation for secondary school students about the basic glossary and the correct use of medication. The pilot study presentation was proved to be successful by feedback: 100% of respondents heard new, useful information, 83% of would take part in similar lecture, 61% prefer to contact a pharmacist for advice. Updated presentations were hold, they proved successful too.

CONCLUSIONS: The proper use of medications has a great impact in aspects of pharmacovigilance. Better knowledge of health and medication-related question among young people achieved by the increase of confidence towards pharmacists in pharmaceutical care would enhance the next generation in safer drug use and health-conscious life to live. Cooperating with schools can be an effective way to educate our future patients.

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P2H-13

Added value of different healthcare professionals, with special regard to pharmacists to COPD therapy experience

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AIMS: This research sets the objective to provide an insight how healthcare professionals and pharmacists can contribute to the well-being of patients. In order to better understand the case, we evoked best practice we used in our RCT and the results of real life patient follow-up interviews

completed after participation in the study. The conducted RCT included n=227 patients.

METHODS: Patients were randomly assigned to the educated group and placebo. A major part of patients were recruited at pulmonology primary care centres. In order to provide a unique therapy experience and to achieve tailored education, patients were given only „draft" information that was also subject to change during their personal education session. As an exit interview we collected data from patients on their perceptions of the healthcare professional, who helped them participate in the study and insights on the quality of the education they received.

RESULTS: Results provide a complex overview methodologically how is it worth educating the patient to enhance the improvement of the PROs. Primary analysis of the data implies that the more you sow, the more you reap: patients educated within the frame of the pilot in the pharmacy appreciated the quality of care more. Apparently, the time invested in their educated multiplied by the end: they show better results in outcomes; though, this can be interpreted as a hint due to the limited number of patients educated in the pharmacy. Patients who took the programme in the pulmonary centre provided robust data and were altogether slightly less satisfied with the education.

CONCLUSIONS: Patients with chronic conditions definitely need more attention, and education is a way to keep them in the loop. In order to convey sticky messages, education needs to be tailored and healthcare professionals need to take time. Pharmacies seem to be an ideal place for education, though patients are harder to recruit and persistence also plummeted more there.

P2H-14

Evaluation of drug safety issues related to pharmacovigilance of PET radiopharmaceuticals in the European Economic Area and efficiency analysis of the risk-management plan

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BACKGROUND: Positron emission tomography (PET) is a noninvasive nuclear medicine related imaging procedure. PET imaging provides the opportunity for diagnostic purposes, monitoring disease progression and response to treatment. The most commonly used radiopharmaceutical is 18F-Fludeoxyglucose (18F-FDG). Radiopharmaceuticals rarely have any pharmacodynamic effects or cause adverse reactions. However, in accordance with Article 106 of Directive 2001/83/EC, sufficient pharmacovigilance system must be obtained.

AIMS: This study has aimed to assess the European database of suspected adverse drug reaction reports (EDSADR) and EMA public assessment reports, not to mention medical literature monitoring (MLM) furthermore to present the necessity of risk-management plan (RMP).

RESULTS: PET scan occurrence was found as 172,95 per 10^5 capita in Hungary and 227,50 per 10^5 capita in the European Economic Area (EEA). After having examined the EDSADR up to May 2017, 52 individual cases of 18F-FDG in EudraVigilance were found (number of cases/age groups in years: 6 /0-2, 1 /3-11, 0 /12-17, 19 /18-64, 23 /65-85, 2 /85<, 1 /not specified). The 86,5% of the cases occurred in the EEA (13,5% in the Non-EEA) and the sex ratio was found as 7:10 female to male. 19 different reaction groups were described. The most common side effects involved skin and subcutaneous tissue disorders (23 cases), general disorders and administration site conditions (16 cases). 48 out of the 52 cases were reported by healthcare professionals and only 4 reports came from non-healthcare professionals. According to the results of the MLM (134 Hungarian and 139 global journals) there are negligible number of findings, but most of them are related to dosimetry.

CONCLUSIONS: Safety profile of PET radiopharmaceuticals was proved as satisfactory. For its further development, the support of patient reporting is required. The work of the QPPV essentially needs to be aided by a nuclear medicine specialist and clinical radiophysicist in the signal management team.

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SATELLITE SYMPOSIUM (IN HUNGARIAN) HOSPITAL PHARMACY – ONCOLOGY

S-1

Innovative and well-tried approaches in treatment of the metastatic colorectal cancer

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BACKGROUND: In the latest 20 years the median overall survival of the metastatic colorectal cancer has been doubled. While various factors could influence this advancement, the improvements in the systemic therapies seem to have mayor role in it. The most recent and evidence based knowledge and recommendations has been collected by ESMO (2016).

RESULTS: Fluoropyrimidine based systemic therapies considered first-line treatments. Bolus fluorouracil (5-FU) containing regimens are not recommended, because combination of 5-FU with calcium folinate seems generally less toxic. Furthermore a cytotoxic doublet with oxaliplatin (OX) or irinotecan or a cytotoxic triplet (5-FU, OX, irinotecan) may also provide opportunities, with regard to the goals and conditions. In the last decade targeted therapies gain significant importance in the treatment of metastatic colorectal cancer, and jet, they indicated in the first-line therapy. To avoid side effects, especially the cumulative toxicity of OX, maintenance therapies have been investigated. The second-line treatments are dependent from the first-line treatment. Ramucirumab and aflibercept are newly approved anti-angiogenic drugs which are recommended in second-line treatment too. As third-line therapy, the recommendations contain a multi-targeted kinase inhibitor, regorafenib, but its side-effects often lead to dose-reduction. A newly approved drug, the combination of trifluridine and tipiracil hydrochloride has been also recommended in the guideline. The trifluridine is an antineoplastic thymidine-based nucleoside analogue and seems effective against 5-FU-resistant colorectal cancer cells too, while the tipiracil hydrochloride can inhibit its fast degradation.

CONCLUSIONS: All in all in the treatment of metastatic colorectal cancer targeted therapies may gathered ground in the therapies, but well-tried treatments and pathways could hold new possibilities.

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S-2

The new era of thalidomide?

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BACKGROUND: Multiple myeloma is one of the most common hematologic malignancy. With the introduction of new therapeutic treatment options the clinical response of patients with multiple myeloma has significantly improved over the past two decades.

AIMS: The presentation gives a comprehensive review about the novel therapeutic agents and regimens based on the recent developments and therapeutic guidelines emphasizing the relevant aspects for the clinical pharmacist.

RESULTS: Thalidomide is a widely used drug at the therapeutic area and it has a well-known history regarding its teratogenicity. The safety profiles of the antimyeloma agents are varying across drug classes and across agents within the same class.

CONCLUSIONS: The overview provides updated information about the therapeutic options of the multiple myeloma with the aim to help in the optimal treatment selection and the management of toxicities, which can lead fewer patients requiring dose reductions, treatment discontinuation and improved outcomes.

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S-3

Adverse reactions of PD1 checkpoint inhibitors in the therapy of malignant melanoma

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BACKGROUND: Az újabb, immunrendszert stimuláló daganatterápiás gyógyszerek esetében, a korábbi kemoterápiáknál ismert súlyos toxikus reakciók helyett, egészen másfajta mellékhatásokkal szembesülünk. A melanoma malignum terápiájában a PD1 gátló kezelés 2015 óta érhető el Magyarországon, hatóanyagai a nivolumab és a pembrolizumab. Ezek a hatóanyagok a T-sejtek aktivitásának fokozásával segítik az immunrendszer tumor ellenes folyamatait. A gyógyszer hatásmechanizmusából következik az immunrendszer eredetű mellékhatások fellépte, amelyek ritkán súlyos mellékhatások is lehetnek.

AIMS: A klinikán PD1 gátló kezelésben részesülő melanomás betegeknél jelentkező adverz reakciók elemzése, a kezelés folyamatos követésével.

RESULTS: Klinikánkon ezidáig 34 beteg részesült nivolumab, és 9 beteg pembrolizumab terápiában. Betegeinken a következő adverz reakciók léptek fel: pneumonitis, hepatitis, pancreatitis, nephritis, hypophysitis, thyreoiditis, dermatitis, vitiligo. A mellékhatások egy 3. fokozatú eset kivételével 1-2 fokozat súlyosságúak voltak (NCI-CTCAE v4 szerint). Az események gyakoriságát tekintve megállapíthatjuk, hogy az irodalomban szereplő adatokhoz képest a vitiligo, dermatitis, thyreoiditis magasabb, a pneumonitis, nephritis és hypophysitis alacsonyabb arányban fordult elő klinikánkon. A mellékhatás megjelenése, a bőrtünetek és a thyreoiditis kivételével, terápiás konzekvenciával járt, 5 alkalommal a terápia átmeneti felfüggesztésére volt szükség, egy esetben pedig a végleges leállításra. A kialakult adverz reakciók közül a dermatitist lokális kortikoszteroidokkal kezelték, a hepatitist, pancreatitist és a két pneumonitist per os szterioddal. A thyreoditis esetében pajzsmirigyhormon szubsztitúcióra volt szükség, míg a hypophysitis esetében per os hydrocortisonra.

CONCLUSIONS: A megfigyelt mellékhatások enyhébbek a hagyományos kemoterápiák toxikus mellékhatásainál (neutropenia, thrombocytopenia). Sok esetben szubjektív panaszok nem hívják fel a figyelmet az esetleges eltérésekre, azaz a betegnek panaszt nem okoz, ezért az egészségügyi személyzettől fokozott figyelmet követel. Az előírt kontrollok rendszeres végzése, a páciens szoros monitorozása elengedhetetlen. A megjelenő problémákat számos esetben terápiás szünet kell, hogy kövesse. A PD1-gátló terápia a tünetek megszűntével folytatható.

S-4

Cardiotoxic effects of oncology therapies – clinical pharmacology aspects

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BACKGROUND: European Society of Cardiology published a report in 2016 about cardiovascular risks of oncology therapies along with methods of prevention and treatment. These therapy induced cardiac problems may lead to death, therefore it is important to pay more attention to them. A clinical pharmacist's special knowledge about medicines can help physicians to deliver safe therapy their patients.

AIMS: By using CATO software, treatments with cardiac risks were collected retrospectively. The cardiac risk was assessed based on ESC's report.

RESULTS: It turned out that the largest quantity of patients are exposed in case of breast cancer based on therapies' side effects. In 2016 we treated 86 patients with breast cancer, using 25 different protocols, all together 111 treatment was delivered. In 94% of cases medicine with cardiac risk was used: trastuzumab (47/111), taxane (46/111), anthracycline (49/111).

CONCLUSIONS: Our presentation represents methods how clinical pharmacist can improve patients' quality of life and longer survival. In our practice no serious cardiac adverese effects was detected in 2016, which is to our hope is because of careful cardiac follow-up.

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S-5

Potential advantages of nutritional status screening and Quality of Life measurements in oncology patients

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BACKGROUND: Quality of life (QoL) questionnaires are widely used in oncology to assess the symptoms and performance of cancer patients. Nutritional status is known to affect the outcome of chemotherapy. Malnutrition and metabolic derangement induced by the disease or the treatment has to be recognized to improve the patients' QoL.

AIMS: To assess the nutritional status of patients in view of their physical and psychosocial condition in the Department of Oncology and Hematology. The study was conducted using the EORTC QLQ-C15-PAL and NRS2002 screening tools. Patients receiving chemotherapy were screened by a clinical pharmacist at the first and all subsequent chemotherapy rounds according to their appropriate protocols. In this study tendencies between nutritional parameters and QoL values are evaluated.

RESULTS: 65 patients were interviewed during a year long period between August 2016 and August 2017. A deterioration in almost every dimension of the QoL questionnaire was found. These results correspond well with the characteristic progression of a malignant disease. The incidence of constipation showed reduction, which can also be an artifact of an increased risk of diarrhea due to mucositis in the gut or the positive impact of enteral nutrition. Regarding psychological factors, tenseness did not change during the assessment, severity of depression though did increase which influences the patients' diet and the complience with enteral nutrition.

CONCLUSIONS: EORTC-C15-PAL is a relevant and easy-to-use tool for bedside pharmaceutical counseling. NRS2002 is a reliable tool for the screening of cancer patients and as a healthcare worker the clinical pharmacist implementing the assessment can improve the perception of physical and psychosocial impairments of patients struggling with cancer. Data from this assessment could offer a basis for clinical pharmacist interventions, preferably running in parallel with the interview process.

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S-6

Professional and economic evaluation of Pharmaceutical Centre of Centralized Cytotoxic Drug Preparation

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BACKGROUND: The Unit of the Centralized Cytotoxic Drug Preparation started its work in May 2016 as part of the Central Clinical Pharmacy in Pécs.

AIMS: Our goal was to integrate all the departments and wards preparing and using chemotherapeutic infusions at the Univeristy of Pécs.

RESULTS: Due to the centralized preparation we could reduce the staff assisting in the prosess. The education of the pharmaceutical technicians, who are part of this program is well-controlled by the pharmacists. Owing to the integrated infusion supply, we can ensure wards a standardized and a higher quality assurance in infusion preparation. The complete documentation referring to the cytotoxic drug therapy is availabe due to a software managed drug preparation of the new laboratory. Based on the interface connection between the software and the wards, the documentation is always up-to-date at the laboratory, the wards and the pharmacy as well. The planned therapies and therapies received by the patients are automatically documented. We have confirmed a decrease in the waste of cytotoxic drugs (about 4% of the whole amount of medicine, ATC L01). The oncology drug cost adjusted to the number of cases decreased by 20% compared to the same timeframe previous year. This is a common result from the optimized drug utilization (the use of the overfilled vials) and the drug price change monitoring.

CONCLUSIONS: The appropiate documentation is important for patient- and medication safety as well. As result of the automated documentation healthcare professionals have less administrative tasks to do. The reduce of expenditures enabled the widely use of closed system transfer device (CSTD) in the laboratory.

S-7

Advantages and disadvantages of biosimilars – safety and pharmacoeconomic aspects

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A large number of the best-selling biological medicinal products are, or will soon be, facing competition from similar medicinal products (biosimilars) in the European Union. Biosimilar drugs are highly similar to an originator product, determined by the same comparability concept that has been successfully in use for several decades to ensure appropriate similarity of biological products before and after a change in the manufacturing process. In the past 10 years, experience has shown that even complex, biotechnologically manufactured compounds can be safely produced with very close similarity, so that no clinically meaningful difference in terms of efficacy and safety is to be expected.

As most biological are used to treat chronic diseases, an intensive discussion is present in the scientific community about the interchangeability of a biosimilar with its reference product, with the main concerns being therapeutic equivalence, tolerability and immunogenicity.

In this presentation, the theoretical basis of the presumed risks of switching is explored based on data already available derived from such practice.

While the evidence in scientific literature to determine the appropriate terms for switching off-patent biologics and biosimilars is scarce, it seems clear that on the basis of current knowledge, it is very unlikely and highly difficult to substantiate that comparable versions of the same active substance approved in accordance with EU legislation on a population level, would have different safety and/or efficacy profiles in individual patients upon a switch. There is, however, also a clear expectation from healthcare professionals that a balanced and watchful approach should be advocated in this manner as it is the prescribers' responsibility to choose an off-patent biologic or its biosimilar tailored to the individual patient's needs.

In this respect, hospital pharmacists should play a key role in the uptake of biosimilars by providing a 'hub of information' to other healthcare professionals with regard to real-world use and evidence base of off-patent biologics and biosimilars.

Policy makers need to also embrace the professional opinion of physicians, pharmacists and other stakeholders in order to design a procurement and reimbursement system that ensures sufficient flexibility in enabling the presriber to act in the best interest of the patient, including the availability of choice between similar products. Tendering schemes should avoid a 'winner takes it all' approach, especially on large, regional/national scales.

In conclusion, this presentation advocates the timely uptake of biosimilar products with a balanced approach, supporting flexible procurement and reimbursement mechanisms and emphasizes the importance of a multi-stakeholder consensus in policy development.

S-8

Parameters associated with nutritional status in hospitalized patients: clinical data analysis

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BACKGROUND: The prevalance of malnutrition in hospitalized patients vary between 30-50%. Undernourishment may lead to poor wound healing, increased morbidity and mortality, which can lead to longer hospital stay and increased health care cost. In our previous study the nutritional status of 121 inpatients was screened by the Nutritional Risk Screening tool recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) in the first quarter of 2016. It was found that 58% of patients were highly and 35% were moderately at risk of malnutrition. Beside questionnaires other information sources can be used to assess parameters that are associated with nutritional status in a hospital setting. However there are several publications regarding the relationship between the nutritional status and clinical outcomes, the analyzis of great amount of clinical data with diverse structure requires novel approaches.

AIMS: Our aim is to determine the prevalence and pattern of malnutrition and compare it with literature data. Furthermore we would like to analyze the clinical data with the tools of „Big Data" Analytics to explore risk factors associated with malnutrition and correlations with clinical outcomes.

RESULTS: The analysis is in progress.

CONCLUSIONS: The results obtained from the „Big Data" anlysis will help to develop clinical decision support tools for comprehensive nutritional assessment of high risk patients during admissions and the optimization of nutrition therapy, as well to establish cost-effectiveness.

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