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Contents

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Acta Pharmaceutica Hungarica – CESPT Edition – Greeting 88. 87 2018.

Greeting

On behalf of the Organizing Committee I am pleased to welcome you among the participants of the 12th Central European Symposium on Pharmaceutical Technology and Regulatory Affairs held in Hungary second time.

The conference series started in 1995 under the patronage of EUFEPS and the goal of the founders was to give a platform for colleagues from the Central European region working on the field of pharmaceutical technology in the industry, universities or academic institutes. In the past conferences the original goals were extended, and the conference topics covered also pharmaceutical biotechnology or as in this conference, the regulatory aspects of drug development and manufacturing.

This scientific forum traditionally gathers colleagues from all over Europe but especially from the Central- and Eastern-European region and serves as a strong and stable background for permanent dialogue between pharmacists and other scientists working in the fields of pharmaceutical R&D or manufacturing.

The conference provides the possibility for the participants to present their results, discuss the new developments and the future directions of the pharmaceutical technology and manufacturing.

It offers a good opportunity to promote scientific achievements for talented young pharmacists, initiate 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 we have 250 colleagues registered for this symposium. The program contains 10 plenary and keynote lectures, 25 verbal and 152 poster presentations.

Looking forward to seeing you in Szeged and having a fruitful and vivid conference!

Assoc. Prof. Ildiko Csoka
President of the 12th Central European Symposium
on Pharmaceutical Technology and Regulatory Affairs

Acta Pharmaceutica Hungarica – CESPT Edition – Committees 87. 88-89 2018.

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Acta Pharmaceutica Hungarica – CESPT Edition – Curriculum Vitae 88. 90-94 2018.

Curriculum Vitae of Invited Speakers

Andreas Bernkop-Schnürch

University of Innsbruck, Austria

Prof. Andreas Bernkop-Schnürch was educated in pharmacy at the Institute of Pharmacy (M.Sc.) and in microbiology and genetics at the Institute of Microbiology and Genetics (D.Sc.), University of Vienna, finishing his doctorate in 1994. In 2003 he was appointed to a chair in pharmaceutical technology at the University of Innsbruck, Austria. From 2006 to 2013 he served as dean of the Faculty of Chemistry and Pharmacy at the University of Innsbruck. His research interest is in the area of mucoadhesive polymers, nanocarriers, peptide drug delivery and self-emulsifying drug delivery systems (SEDDS). He developed thiolated polymers (thiomers) and zeta-potential changing nanocarrier systems. Dr. Bernkop-Schnürch is author of over 370 research articles and reviews as well as editor and (co-)author of several books. He is the founder of Mucobiomer GmbH (now part of the Croma-Pharma Holding), Thiomatrix GmbH and Green River Polymers GmbH.

Andreas Zimmer

Karl-Franz University of Graz, Austria

Prof. Andreas Zimmer (1963) studied Pharmacy at the Johann Wolfgang Goethe-University Frankfurt am Main, Germany. He stayed with a PhD program and did part of the work which focused on the evaluation of nanoparticles as ophthalmic drug delivery systems at the University of Wisconsin with Joe Robinson, Madison WI, USA. After the PhD at Jörg Kreuter's lab in Frankfurt he continued with a university career at the Biocenter at the University of Frankfurt in the field of drug delivery and pharmaceutical nanotechnology. 1999 he joined the group of Robert Gurny in Geneva, Switzerland, as guest scientist and from 2000 on he moved to the University of Graz, first as guest lecturer and later as full professor. Since 2004 he is leading the Department of Pharmaceutical Technology and Biopharmacy at the Karl-Franzens-University in Graz, Austria. His research is focused on drug delivery and drug targeting devices and specialized on nanoparticles used for DNA- and RNA-drugs as well as for peptides and proteins.

Chris Vervaet

Gent University, Belgium

Prof. Chris Vervaet is head of the Laboratory of Pharmaceutical Technology (Faculty of Pharmaceutical Sciences, Ghent University, Belgium), a research group focusing on the development and characterization of pharmaceutical solid dosage forms (granules, tablets, pellets, sustained release matrices). Over the last 10 years continuous manufacturing of solid dosage forms has been the one of main research topics of the team of Prof. Vervaet, focusing on processes such hot-melt extrusion, injection molding, wet granulation, tableting and blending. By evaluating the impact of formulation and process parame-

ters on the performance of these continuous processes key information was obtained to smoothen the transition within the pharmaceutical industry from batch processing to continuous manufacturing. By combining the expertise of the Laboratory of Pharmaceutical Technology with the implementation of PAT tools during continuous manufacturing (in collaboration with Prof. De Beer, Laboratory of Pharmaceutical Process Analytical Technology, Ghent University) a better insight into the fundamental material behavior during continuous manufacturing was gained. This has resulted in multiple international collaborations, at an academic level as well as with large and small pharmaceutical companies. About 100 research papers have been published by the research group of Prof. Vervaet on the topic of continuous manufacturing of pharmaceuticals.

Jörg Breitkreutz

Heinrich Heine University, Düsseldorf, Germany

Prof. Jörg Breitkreutz studied Pharmacy from 1987 to 1991 at the Westphalian Wilhelms-University of Münster, Germany. He finished his PhD in 1996 at the Institute for Pharmaceutical Technology and Biopharmaceutics in Münster under supervision of Prof. Rüdiger Gröning. From 1996 to 1997 he joined Thiemann Arzneimittel GmbH in Waltrop, Germany, as the head of Product Coordination. In 1997 he went back to the university in Münster to work on his habilitation thesis (2004) on pediatric drug formulations. In 2004 he became professor for pharmaceutical technology at the Institute of Pharmaceutics and Biopharmaceutics at the Heinrich-Heine-University in Düsseldorf, Germany, and today is the director of this institute. Joerg Breitkreutz serves as external expert for various regulatory bodies and companies. He is presently heading the Paediatric Formulation group at the European Directorate for the Quality of Medicines and Healthcare (EDQM). Since 2010 he is president of the non-for-profit International Association of Pharmaceutical Technology (APV). His research focuses on pediatric and geriatric drug formulations, drug printing technologies, orphan drugs, process analytical technologies, green and sustainable medicinal products.

Katalin Varjú

ELI–ALPS Research Institute, Hungary

Dr. Katalin Varjú started her physics education graduating with a diploma in physics with distinction from the University of Kent, Canterbury, UK in 1996, followed by a MSc in physics with distinction at JATE University, Szeged, Hungary in 1999. She graduated with a theoretical physics PhD from the University of Kent in 2000.

She has worked at the University of Szeged, from 1999, where she holds now an associate professorship, leading a research group, and teaching actively. She has been a visiting scientist at Lund University in Sweden (2003-2005) in the Marie Curie Programme. She habilitated at the University of Szeged in 2015.

Dr. Varjú has been working for the ELI programme from the beginning. She was active in the preparatory stages of the ELI proposals (ELI PP and ELITRAIN ITN) and co-edited the first Scientific Case for ELI-ALPS in 2011. She is currently the head of the Attosecond Sources Division responsible for developing the attosecond pulse secondary sources.

She has published 52 papers in refereed journals, has been cited 1175 times, her h-index is 17.

Her main research interests are in optical and atomic physics: concerning the propagation of femtosecond laser pulses, high-order harmonic generation and attosecond pulse (train) generation.

Niklas Sandler

Åbo Akademi University, Turku, Finland

Prof. Niklas Sandler received his M.Sc. (Pharm.) in 1998 from University of Helsinki, Finland. He got his Ph.D. in pharmaceutical technology from the University of Helsinki 2003. He was lecturer at the Pharmaceutical Technology Division, Helsinki between 2003-2005 and in 2005-2006 he was a postdoctoral researcher at the University of Otago, New Zealand, focusing on research on solid-state characterization of drugs. He became an adjunct professor in Pharmaceutical Technology at the University of Helsinki in 2007. Between 2006 and 2008 he had a senior researcher position at AstraZeneca, Pharmaceutical and Analytical R&D in the UK. From September 2008 until July 2009 was a temporary professor in Industrial Pharmacy at the University of Helsinki. Since August 2009 he has been full professor in Pharmaceutics at Åbo Akademi University (ÅAU), Turku, Finland and heads the research group in drug-delivery and pharmaceutical technology. He has pioneered in research around printable drug-delivery systems. The current aim of his research group is to increase the understanding of material behaviour in fabrication of printed drug-delivery systems and to explore various printing techniques in drug manufacture. He is the president of the Finnish Pharmaceutical Society since 2012. Vice rector responsible for research affairs and innovations of Åbo Akademi University since 2015. He is the president of the Finnish Pharmaceutical Society since 2012. He has been an Executive Board Member of EUFEPS from 2013 onwards.

Márk Oláh

Gedeon Richter Plc., Hungary

Dr. Márk Oláh is a medical project manager at Richter Gedeon Plc. since 2014, focusing on original drug development in the central nervous system (CNS) field, including global medical coordination and clinical support for drug research and development. He is an active contributor to the in-house original CNS medical strategy, including target product profile development, indication portfolio development, and competitive landscape analysis. He received his M.D. in 2002 from Semmelweis University in Budapest, and began his early medical carrier as a clinical physician in the 2nd Department of Internal Medicine. In 2011, he obtained his Ph.D in neuroscience, with particular interest in the neuro-endocrine molecular regulation of pituitary hormone secretion. He was an assistant professor in the Department of Anatomy, Histology and Developmental Biology at Semmelweis University. In 2011-2012 he continued his professional career with a postdoctoral visiting fellowship at the National Institutes of Health (USA), where he studied the transcriptional regulation of pituitary and adrenal hormone secretion during the stress reaction, both in vivo and in vitro. He is committed to all clinical fields of personalized medicine as an active member of the Hungarian Personalized Medicine Society.

Odon Planinšek

University of Ljubljana, Slovenia

Prof. Odon Planinšek has finished his studies as pharmacist (M.Sc) at the Faculty of Pharmacy, University of Ljubljana in 1996. He recieved PhD degree in 1999 on the same University. He is working in the Department of Pharmaceutical Technology since 1994. He became assistant professor in 2001, associate professor in 2006 and since 2012 he is a full pofessor of the Department of Pharmaceutical Technology. In 2001 and 2002 he performed postdoctoral studies in University of London, Faculty of Pharmacy. He is a member of the Slovenian Pharmaceutical Society and between 2005 and 2015 he served as associate editor of the Acta Pharmaceutica journal. His main research interest is preformulation, deformulation and formulation of solid paricles and tablets.

Piroska Szabó-Révész

University of Szeged, Hungary

Prof. Piroska Szabó-Révész has got her diploma as pharmacist in Albert Szent-Györgyi Medical University of Szeged in 1975. She has got her university doctorate in the same University in 1979 and in the same year she became a specialist pharmacist in pharmaceutical technology. She has got her PhD degree in Semmeweis University, Budapest in 1992. She has done her habilitation in Albert Szent Györgyi Medical University of Szeged in 1996. She became the Doctor of Sciences (D.Sc.) in 2006. She was nominated as full professor in 2004 and served as the Head of the Department of Pharmaceutical Technology, University of Szeged between 2005 and 2016. She is the Head of Pharmaceutical Technological Program at the PhD School for Pharmaceutics and Chair of the Habilitation Committee of the Pharmaceutical Sciences in University of Szeged. She is the Head of the Nanotechnological research team at the Institute of Pharmaceutical Technology and Regulatory Affairs. She was the supervisior of 16 PhD thesis and 25 diploma works. She is doing reviewing activity for 10 journals. She is the leader of numerous national and international projects. She has given 130 lectures at national and international scientific events, participated in more than 60 industrial research-development projects, was the author of 3 books, 10 book chapters, 3 university hand-outs, 221 papers and 2 patents Her main fields of interest are particle engineering, micronization, nanonization and amorphization of crystalline pharmaceutical agents, solid-phase analysis, development of drug delivery systems for nasal and pulmonary administration.

Sarah Barthold

Glatt Pharmaceutical Services GmbH & Co. KG

Dr. Sarah Barthold has studied pharmaceutical sciences at the University of Regensburg and ETH Zurich before she finalized her education with a PhD in Pharmaceutical Technology at the Helmholtz-Institute of Pharmaceutical Research Saarland/Saarland University.

From 2015 to 2017 she worked at the institute of Biopharmacy and Pharmaceutical Technology at Saarland University dealing with nanoparticulate dosage forms.

In 2017 she joined Glatt GmbH as project manager in the Pharmaceutical Development Division of Glatt Pharmaceutical Services Binzen / Germany.

Glatt Pharmaceutical Services activities include the pharmaceutical development of solid dosage forms with a focus on multiparticulate dosage forms and controlled release applications.

Tamás L. Paál

National Institute of Pharmacy and Nutrition and University of Szeged, Hungary

Prof. Tamás L. Paál graduated in Pharmacy, postgraduated in drug control and chemical engineering then received his Ph.D. at different Universities, all in Budapest. Having worked 11 years for the Hungarian pharmaceutical industry he joined the National Institute of Pharmacy, the Hungarian medicines regulatory authority in 1978. He was Director-General of the Institute between 1984 and 2008. Having been retired he has been scientific adviser of the agency (now National Institute of Pharmacy and Nutrition). He has been promoted Professor in 1984. He has worked in the Postgraduate Medical University then the Semmelweis University, Budapest until his retirement in 2013. Parallelly he was invited to create the Institute of Drug Regulatory Affairs at the Faculty of Pharmacy, University of Szeged and directed this between 2002 and 2008. He became Professor emeritus (at present at the Institute of Pharmaceutical Technology and Regulatory Affairs) in 2013. He worked on different regulatory missions for UNIDO, WHO and the EU PHARE Project in Central America, Central Asia, Africa and Eastern Europe. He received, among others, the Life-long membership award from TOPRA (The Organisation of Professionals in Regulatory Affairs) and was awarded also by DIA (Drug information Association) and RAPS (the Regulatory Affairs Professionals Society). He is member of the European Academy of Sciences and Arts. He published 230 papers, mainly on chemistry and regulatory affairs.

Acta Pharmaceutica Hungarica – CESPT Edition – Plenary Lectures 88. 95-101 2018.

Plenary Lectures

PL-1

The Changing Landscape of Personalized Medicine

OLÁH, M.

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Personalized medicine has the potential to profoundly improve medical treatment. Until now, most medical treatments have been designed for the "average" patient. As a result of this "one-size-fits-all" approach, treatments can be very successful for some patients but not for others. Personalized (precision) medicine is an innovative approach that takes into account individual differences in people's genes, environments, and lifestyles. It gives medical professionals the required resources to target specific treatments of the illnesses, tailored to specific characteristics, such as a person's genetic makeup, or the genetic profile of an individual's tumor. For instance, varied phenotypes may exist which have a single underlying genetic variant leading to a possibility of a single personalized targeted therapy.

The European Commission has recently addressed the policy perspective on personalized medicine, aiming for a paradigm change in healthcare. Personalized approaches face multiple challenges today, including technology and know-how. Next-generation sequencing is one of the most widely used methods in personalized medicine, generating gigabytes of data from each patient. Beyond collection, storage, and availability of genetic and clinical data, further ethical, social, and legal concerns have emerged during the last decade.

We will also provide a global update on the current clinical achievements, and on newly marketed innovative products in different indications. We will pay special attention to orphan diseases and the clinical reclassification of patient populations in contrast to previously used diagnostic approaches, which were based mainly on the phenotype. Furthermore, we demonstrate the possibilities of implementing personalized medicine aspects into future industrial drug research and development.

PL-2

Regulatory approach in the pharmaceutical R&D

PAÁL, T. L.

Institute of Pharmaceutical Technology and Regulatory Affairs, Faculty of Pharmacy, University of Szeged, Szeged, Hungary

While diverse definitions of regulatory science can be found in the literature they agree that the target of this applied science is to develop and adjust drug investigation methods to regulatory needs. Differences in the performance of regulatory science between the academic and regulatory (at the same time: industrial) researchers in relation to their aim, starting points and target are pointed out. The basis of the academic research is the scientific literature while regulatory requirements appear in the hard (mostly indirectly) and the soft laws (guidelines) as well as in the current regulatory practice (the latter is mostly neglected by the academic research). This is illustrated by the European Union rules governing medicinal products. The aim of the academic research is to produce always something new while regulatory requirements expect working strictly in line with the guidelines unless a very good reason is proven. However, the regulatory world needs the academic medicine research directed to new methods as well as the latter needs the incorporation of the regulatory thinking. The solution could be a careful combination of the two approaches and selection of research topics giving priorities to those of recent regulatory interest.

The first example originates from the European "regulatory sameness" fiction (different salts, esters, etc. of active principles as well as similar immediate release dosage forms can be "the same" and bioequivalent). By contrast, "suprabioavailability" (often target of technological research) may not permit the "generic", only the "hybrid" route of authorisation, offering not more than a reduced amount of the active principle in the dosage-form with its price gain plus less environmental exposition. The benefit of "suprabioavailable" substances should be evaluated case-by-case.

The second example covers bibliographic (well-established use) applications when the relevance of literature data of the already marketed, similar

medicines to the claimed product must be proven. This is simple for BCS I and III active principles, but the recent regulatory practice is more demanding in case of BCS II and IV ones. Limitations of the present dissolution test methods and the way of the possible solution is discussed.

KN-1

ELI ALPS – The next generation of attosecond sources

VARJÚ, K.

ELI-ALPS Research Institute, Szeged, Hungary

The Extreme Light Infrastructure – Attosecond Light Pulse Source (ELI-ALPS), the Hungarian pillar of ELI, is the first of its kind that operates by the principle of a user facility, supporting laser based fundamental and applied researches in physical, biological, chemical, medical and materials sciences at extreme short time scales.

This goal is realized by the combination of specialized primary lasers which drive nonlinear frequency conversion and acceleration processes in more than twelve different secondary sources. Any light pulse source can act as a research tool by itself or, with femtosecond synchronization, in combination with any other of the sources. Thus a uniquely broad spectral range of the highest power and shortest light pulses becomes available for the study of dynamic processes on the attosecond time scale in atoms, molecules, condensed matter and plasmas.

The ground-breaking laser systems together with the subsequent outstanding secondary sources generate the highest possible peak power at the highest possible repetition rate in a spectral range from the E-UV through visible and near infrared to THz. The facility – besides the regular scientific staff - will provide accessible research infrastructure for the international scientific community user groups from all around the world.

The attosecond secondary sources are based on advanced techniques of Higher-order Harmonic Generation (HHG). Other secondary sources provide particle beams for plasma physics and radiobiology. A set of state-of-the-art endstations will be accessible to those users who do not have access or do not wish to bring along their own equipment.

The realization of the ELI-ALPS facility has commenced recently with the inauguration of the new building complex in May 2017. Step by step the lasers are now commissioned, trialed and handed over for user operation.

REFERENCE:

1. Kuhn S. et al. Journal of Physics B. 50, 132002 (2017)

KN-2

Are printing technologies completely changing drug manufacturing of the future?

SANDLER, N.

Pharmaceutical Sciences Laboratorym Åbo Akademi University, Turku, Finland

Different types of printing methods have attracted interest as emerging technologies for fabrication of drug delivery systems (DDS). Examples from the past decade include the use of diverse types of inkjet (IJ) printers. for depositing drug-loaded inks to produce accurately and precisely dosed units of active pharmaceutical ingredients (APIs). Furthermore, the exploitation of extrusion based printers and a combination of technologies has been reported. Different additive manufacturing technologies or three-dimensional printing approaches also play an integral role in future fabrication scenarios. Many types of options for printed dosage form exist. The concepts include on the simplest level accurately deposited doses of drug substances and one-layer films. On the other hand, printing technologies allow the manufacture of advanced multi-layer membranes, various type of stacked systems, and integrated multi-compartment systems with bioactive components. These can comprise of integrated combinations of diverse materials to form sophisticated bio-functional constructs. Moreover, computer aided design allows endless opportunities to create suitable geometries with tailored functionality e.g. through controlling the release properties of one or multiple drug substances. This talk will present examples on the use of printing technologies that are of potential interest in printing of bioactive substances. Many of ideas in the use of this type of technology in drug manufacturing is based on the ideas that development and fabrication of pharmaceuticals in a tailored manner to meet some of the foreseen personalization needs of treatments for patients. This optimally means more possibilities to accomplish on-demand fabrication of custom-made medications. This talk will

present examples on the use of printing technologies that are of potential interest in personalization of drug products and future manufacturing.

KN-3

Oral peptide drug delivery: What intestinal barriers fear the most

BERNKOP-SCHNÜRCH, A.

Institute of Pharmacy, University of Innsbruck, Innsbruck, Austria

Oral delivery of peptide drugs is a great challenge as various barriers being encountered with the GI-tract have to be overcome in order to reach the systemic circulation. Especially the enzymatic barrier (I) being based on secreted and membrane bound peptidases, the sulfhydryl barrier (II) causing unintended thiol/disulphide exchange reactions between thiols being present in the GI-tract and peptide drugs, the mucus gel barrier (III) restricting peptides and formulations containing them from reaching the absorption membrane and the absorption membrane barrier (IV) are responsible for a comparatively poor oral bioavailability. To overcome these barriers, numerous strategies including structural modifications of peptides in order to improve their stability towards peptidases, enzyme inhibitors, permeation enhancers, multifunctional polymers and different nanocarrier systems were adopted. Among these strategies in particular self-emulsifying drug delivery systems (SEDDS) have received considerable attention within recent years. Despite their hydrophilic character therapeutic peptides can be incorporated in the lipophilic phase of SEDDS via complexation with lipophilic excipients that are mainly surfactants. Due to such complexations the lipophilic character of peptides can be even 100,000-fold increased. Once emulsified in the GI-tract to oily droplets in the size of 30-200 nm, SEDDS provide a protective effect towards peptidases as digestive enzymes are too hydrophilic to penetrate the oily droplets and to reach the incorporated peptide drug. By contrast to co-administered enzyme inhibitors, the risk of any formulation derived side effects can be excluded. As sulfhydryl bearing nutrients and endogenous glutathione can also not penetrate the oily droplets, the incorporated peptide drugs are protected towards their attack. Moreover, in order to overcome the mucus gel barrier the oily droplets can be made highly slippery. In particular the use of PEGylated surfactants assembling on the surface of the oily droplets makes them mucoinert and mucus permeating. Having reached the absorption membrane, the improved lipophilic character of the peptide drug having been obtained via complexation with lipophilic excipients can now show its real potential. Due to the raised lipophilic character peptides can more easily permeate the absorption membrane and reach the systemic circulation. The great potential of the SEDDS-technology for oral peptide drug delivery could meanwhile be demonstrated via various in vivo studies showing an oral bioavailability around 10%. According to these recent developments and results, SEDDS can be regarded as game changing approach for oral peptide drug delivery.

KN-4

Drug Delivery of microRNA

ZIMMER, A.

Institute of Pharmaceutical Sciences, Department of Pharmaceutical Technology and Biopharmacy, University of Graz, Graz, Austria

INTRODUCTION: More than two decade has passed since the discovery of RNA interference, followed by exploration of the first non-coding microRNA (miR) and endogenous so called small interfering RNAs (siRNAs) [1]. Since these major findings the field of microRNA biology has expanded considerably and the roles of miRs in pharmaceutical development and disease application have made miRs attractive tools and APIs as antimiRs for novel therapeutic approaches. In addition, up to now about 194 clinical studies were conducted with focus on miR and since about 10 years all together 682 clinical trials were initiated in the field of cancer, auto-immune diseases, respiratory- and infectious diseases, such as hepatitis and others (ClinicalTrials.gov).

MATERIALS AND METHODS: During drug development it soon became obvious that miRs as unmodified RNA in naked form is not suitable for a systemic application due to rapid degradation or insufficient PK/PD properties. Therefore, in early studies strategies for chemical modification as well as formulation with drug carriers were investigated. During this lecture I will give an overview about current delivery methods which will include also drug targeting strategies

to improve the efficacy of the miR-therapeutics. These include non-viral carries such as liposomes and lipid-nanoparticles, polymeric nanoparticles and combinations between lipid and polymeric carries, as well as metal nanoparticles and in opposite, more biology driven vehicles like exosomes.

RESULTS: Due to the increased complexity of the drug formulation the combination of two rather new ingredients, the miR and the drug carrier, in early studies chemically modified miRs were applied. Santaris, now a part of Roche was leading the field with so called locked nucleic acids (LNAs). However, also liposomes which were used as drug carriers for cancer medication before, reached clinical trials. Focusing on cancer application Mirna Therapeutics investigated liposomes as miR carriers. Further, miR-145 is a current example for such miR-liposomal formulation. In this case, a complex between protamine, a cationic DNA binding peptide and the miR-145 followed by packaging into liposomes was shown in 2016, a strategy which was originally investigated and published by our research group for the first time in 2005. Other drug delivery polymers like polyethylenimin, dendrimers or biopolymers like chitosan are reported as potential miR carriers. Examples of our research will be also shown and will demonstrate the potential application of miR-27 in lipid metabolic diseases.

REFERENCES:

1. Fire, A. et al. Nature 391, 806–811 (1998)

KN-5

Particles design and solid dosage forms

PLANINŠEK, O.

Chair of Pharmaceutical Technology, University of Ljubljana, Ljubljana, Slovenia

Particulate formulations represent a large proportion of pharmaceutical products and the concept of engineering materials with improved properties is widely applied in pharmaceutical technology. The performance of these products is a function of their composition, but also of their particulate structure, properties, and attributes. We need to understand and control a range of key unit manufacturing operations such as crystallization, milling, granulation, powder mixing and compression which can be very challenging. Particles are being designed especially as powders for direct compression and for dry powder inhalers. Their optimization lead to decrease of production costs (improved processability) and desired active pharmaceutical ingredient (API) performance. It is expected that optimal drug delivery system transport a selected medication through a specific path in a live body to reach an organ and react there at a desired rate. There are continuous efforts to improve every single step of the process of its formulation. Desired properties of particles incorporated into solid dosage forms can be achieved with different top down and bottom up methods. Obtained particles can be composed of single, two or more components which can be API(s), excipient(s) or their combination. Particles are being designed also from the molecular structure point of view with the emphasis on oral bioavailability of poorly water-soluble APIs enhancement. Beside traditional crystal modifications approaches, salt or hydrate formation co-crystals and co-amorphous systems gained significant attention recently. In the lecture some interesting concepts of particles design that can be relatively simply transferred to industrial scale such as spherical crystallization, precipitation of particles in microfluidic reactor and continuous heterogeneous crystallization on excipient surfaces will be presented.

KN-6

CONTINUOUS PROCESSING OF SOLID DOSAGE FORMS

VERVAET, C.

Department of Pharmaceutical Technology, Gent University, Gent, Belgium

Over the past decade significant advancements have been made to support the implementation of continuous manufacturing of dosage forms within the pharmaceutical industry. Continuous processing is considered as an essential aspect to modernize pharmaceutical manufacturing as this concept - compared to traditional batch manufacturing- provides several opportunities to improve product quality and to increase manufacturing flexibility: shorter production times, smaller footprint, faster product development, on-line product monitoring and control, enhanced process understanding, real time release, … Continuous manufacturing also allows to easier accommodate supply needs as production volume can be increased

without scale-up issues since it is controlled by time, not equipment.

As a result several newly engineered fully integrated continuous manufacturing lines of solid dosage forms have been introduced by equipment vendors, e.g. integrated powder-to-tablet lines linked all unit operation into a single continuous process. This presentation presents some of these concepts and highlights some of the essential aspects that must be covered to ensure the successful introduction of a continuous manufacturing line within the pharmaceutical industry (e.g. material residence time distribution throughout the continuous manufacturing line, implementation of Process Analytical Technology (PAT) for process monitoring and feed-back/feed-forward process control, potential of surrogate approach during initial process development).

KN-7

Modifying the physicochemical properties of NSAIDs for nasal administration

SZABÓ-RÉVÉSZ, P.

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

The presentation summarizes the nasal delivery of NSAIDs (non-steroidal anti-inflammatory drugs) for fast onset analgesia and for the potential prevention of Alzheimer's disease. It will be discussed how the physicochemical properties of NSAIDs can be modified with respect to the biological characteristics of the target site and what innovative technology and/or nasal compositions can promote an effective therapy.

Intranasal administration is a potential route of delivering NSAIDs through the trans-epithelial absorption into the systemic circulation ("nose-to-blood") and/or central nervous system (CNS) through the blood-brain-barrier. NSAIDs can be delivered directly from the nasal cavity into the CNS through the axonal transport ("nose-to-brain").

NSAIDs are poorly dissolved at the nasal membrane (pH: 5.3-5.6), increasing their solubility and/or the rate of dissolution is a challenge to overcome in the development of nasal dosage forms, in order to enhance bioavailability. Solubility may be improved by using salt forms, solubility-enhancing or complexing agents. The dissolution rate may be increased by particle size reduction or by breaking of crystal structure (amorphous form, applicable for a liquid or gel form containing the suspended active agent). Also, the residence time, i.e. the length of time the formulation spends in the nasal cavity should be lengthened by using mucoadhesive agents.

Nanotechnology is a new opportunity for the above considerations. Reducing the particle size to the nano range and researching and developing nanostructured units can help the successful nasal application of NSAIDs.

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IL-1

Drug delivery in the pediatric and geriatric patient population – speaking about multiparticulates

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During lifetime, abilities and capabilities change from age to age. Children and elderly people have special needs that should be addressed when thinking about oral drug product development. Visual, motoric, and swallowing capabilities are amongst the major age-related changes. Multiparticulates, covering micropellets, pellets and mini-tablets thus present a feasible approach for convenient and patient friendly medication. Moreover, one bulk formulation offers the possibility of a broad range of final drug products, applying well-established manufacturing technologies at viable cost.

The rationale of multiparticulate formulations and associated manufacturing technologies will be demonstrated and explained with a focus on (micro)pellets. Time permitting, one development project will be shown as case study with regards to the idea and the technological realisation of a multiparticulate formulation for the treatment of a rare disease in the pediatric population, starting from patient's needs until market launch.

SP-1

Non-destructive quantification of impurities in 100 mg pharmaceutical samples using energy-dispersive X-ray fluorescence (EDXRF)

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INTRODUCTION: Energy-dispersive X-ray fluorescence (EDXRF) is a versatile technique for qualitative and quantitative elemental analysis, typically without the need for complicated sample preparation steps. It has been used in many industries for years but has only recently been accepted by the Pharmaceutical industry with the implementation of USP [1]. Pharmaceutical laboratories often struggle with small sample masses, especially during development. Elemental quantification by EDXRF with small sample masses requires long measurement times, often making it impractical for routine operation. Recent advances in EDXRF technology have yielded significant improvements in sensitivity. Our work demonstrates that these improvements now allow the non-destructive quantification of 17 impurities in pharmaceuticals in 1 hour or less, using only 100 mg of material [2].

MATERIALS AND METHODS: Measurements were performed with an Epsilon 4 EDXRF spectrometer, equipped with a 15 W, 50 kV silver (Ag) anode X-ray tube and an SDD30 silicon drift detector. Loose powder standards and routine samples (100 mg) were placed in special small-mass sample cells, assembled using 6 μm polypropylene films. Calibrations for Cd, Pb, As, Hg, Co, V, Ni, Tl, Pd, Ir, Rh, Ru, Se, Pt, Mo, Cu and Cr were developed using in-house cellulose standards. All measurements were performed in air, with a total measurement time of 1 hour per sample.

RESULTS: We were able to demonstrate that the Epsilon 4 EDXRF spectrometer meets the acceptance criteria for calibration linearity, accuracy and specificity, repeatability, intermediate precision, quantitation limits and robustness specified by USP. In addition, the set of calibration standards allows for the development of wide calibration ranges. We were also able to demonstrate LOQ values lower than those specified by ICH Q3D [3] based on 1 g daily doses for all of the included impurities and Calculations suggest that the ICH Q3D criteria could also be met with a 21-minute measurement time.

CONCLUSION: Thanks to swift technological development, EDXRF has become an effective and compliant tool for the analysis of impurities in pharmaceuticals where only small masses are available.

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SP-2

Safe Handling of Cytostatic Drugs

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The handling and production of Hazardous Drugs, like Cytostatics, requests cautious preparations to prevent the contamination of the sample and have a proper protection of the handling staff.

For the protection of the product, it is essential to have a barrier against any contamination agent by the handling personnel, but it is also equally important to provide a barrier for the handler against the dust, mist created by the handling of cytostatic raw materials.

The Personal Protective Equipment must fulfil both functions, it must protect the product and the handler and it should not make the work process harder or make the productivity worth.

Strict standards are used in the clean environments and strict regulations regulate the handling of dangerous chemicals (QuapoS - Quality Standard for the Oncology Pharmacy - defines the requirements for the Personal Protective Equipment).

The best balance between the protection of the product and the handling personnel offered by DuPont™ Tyvek® products through the widely used solutions, as they offer dust and liquid repellence and breathability, which increase the comfort through the day of usage.

The material of Tyvek® provides a protective barrier by its own structure, not like the microporous film or the SMS material, that›s mean that the rapid hand movements and continuously abrasion in the armpit do not decrease its protective properties.

The Tyvek® does not lint, so it fulfils the requirements of cleanroom regulations GMP C/D, ISO 7/8/9 without any cleaning necessary.

The DuPont™ Tyvek® material was tested against many cytostatic drugs and it reached the highest 6/6 class measured by independent laboratories, currently, this is the only one garment, which gives a proper protection against the cytostatics.

The market leader DuPont™ Tyvek®, the cleanroom tailor-made Tyvek® based solution IsoClean® and the most robust, Tyvek® based Tychem chemical protective garments provide the greatest protection and comfort for 50 years.

SP-3

Balancing Competing Requirements of Dose Form Robustness, Disintegration Time and Organoleptics when formulating ODTs with high doses of API.

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INTRODUCTION: Orally Disintegrating Tablets (ODTs) are a well-established dosage form that improve patient convenience. Most of these commercialized products are low dose and/or reasonably palatable without need for substantial taste masking. However for drugs with doses greater than 100mg the formulation challenges increase as the formulator strives to ensure the CQA's of the ODT are maintained and the organoleptic aspects of the dose form remain pleasant. This study investigates the relationship between drug loading and tablet CQA's (Tensile Strength, Disintegration Time and Friability) and relates them to practical targets that go beyond those discussed in the FDA Guideline[1] for the specific challenge related to higher dose API tablet formulation.

MATERIALS AND METHODS: ODT formulations based on the ODT platform Pharmaburst® and the taste masked API paracetamol (Actimask®) were compressed on a Styl'One™ evolution fully instrumented single punch tableting instrument. A study of the compression characteristics was performed on Styl'One using the Analis™ software. True density of each formulation was measured using a helium pycnometer which with the other dimensional data obtained enabled tablet porosity to be calculated and analysed. Formulations were blended for 10 minutes in a Turbula Mixer prior to compression. The formulations were compressed and the resultant tablets were then assessed for the CQAs. TS was calculated by measuring thickness, diameter and hardness on a WHT tester. Friability and DT were obtained according to the USP Methods.

RESULTS: The results show that meeting a DT target of 30 seconds and retaining sufficient tablet robustness is challenging, especially as the API dose exceeds 125mg. However by careful formulation design and use of higher porosity systems such as Pharmaburst acceptably robust tablets can be formulated that have DT's around the 30 sec target.

CONCLUSIONS: Detailed understanding of the tableting profiles and rapid formulation screening is necessary for successful development of this more challenging group of ODT's.

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Oral presentations

OP-1

Speed it up, slow it down – bicalutamide release from 3D printed tablets

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INTRODUCTION: The current 3D printing achievements in the field of pharmaceutical technology include the preparation of various personalized dosage forms and drug delivery systems with accelerated or controlled release of API [1]. Fused deposition modelling (FDM) is a low-cost 3D printing technique which has shown a lot of potential to manufacture drug formulations with desirable drug release profile.

The aim of this study was to evaluate the possibility of obtaining 3D-printed bicalutamide tablets with desired release characteristics by co-extrusion of API-loaded water soluble filament with a non-soluble drug free filament as well as physicochemical characterization of the printed tablets.

MATERIALS AND METHODS: Bicalutamide (BCL, Hangzhou Hyper Chemicals Ltd., China) was used as a model drug substance and Kollicoat ® IR (BASF, Germany) was used as a filament forming polymer. The BCL-loaded filament was prepared by hot-melt extrusion with Noztek® Pro filament extruder (UK) at 175 °C. Commercially available PLA filament (3D Color, Poland) was admixed by co-extrusion at the printing stage to modify the API dissolution. ZMorph® 2.0 SX 3D printer (Poland) was used to produce tablets. Dissolution studies were performed with paddle method in either sink or non-sink conditions using Vision Elite 8 (Hanson Research, USA). Samples were analyzed spectrophotometrically at λ=272 nm using a Shimadzu UV-1800 (Japan). Crystallinity of the API was determined using XRPD studies with Rigaku Mini Flex II (Japan).

RESULTS: The filaments with crystalline BCL were successfully produced for FDM 3D printing, however the partial amorphization was identified after printing stage. The non-sink dissolution studies confirmed that it enhanced the dissolution of BCL from 3D-printed tablets. Co-extrusion with different amounts of PLA filament resulted in controlled release tested the sink conditions. The physical and mechanical properties of filaments and tablets were also evaluated.

CONSLUSION: 3D printing can be successfully utilized to modify BCL release from tablets prepared from feedstock filament by either API amorphization or co-extrusion with insoluble filament to from a mixed matrix.

ACKNOWLEDGEMENTS: Authors acknowledge Polish Ministry of Higher Education and Science for the financial support.

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OP-2

Production of Highly Drug-Loaded Orodispersible Films Using Extrusion Based 3D-Printing

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INTRODUCTION: 3D printing and orodispersible films (ODFs) show potential for individualized medicine. The main disadvantage of the common production of ODFs is the low drug loading [1]. Aim of this study was to produce high drug loaded ODFs via 3D printing.

MATERIALS AND METHODS: Levetiracetem as model drug, polyvinylalcohol/polyethylene glycol copolymer, glycerol and purified water were used to form a semi-solid printing formulation.

Design and Extrusion based 3D printing of ODFs

ODFs (6 cm^2) were designed using 3D-CAD-software Inventor (Autodesk). Two different designs were chosen: 0.35 mm (1 Layer) and 1 mm (2 Layer) distance between the printed strands. In case of the one layered ODF the structure is printed completely without any pores whereas for the

two layered ODFs the single strands are printed in 90° to each other and results therefore in regular pores. ODFs were printed using 3D-Bioplotter (EnvisionTec) with 4.5 bar, printing speed of 30 mm/s and layer thickness of 0.2 mm.

Uniformity of mass and thickness

10 ODFs were weighed and the thickness was determined using micrometer screw (Mitutoyo).

Mechanical properties and Disintegration time

Tensile strength and elongation to break were calculated using texture analyzer (Stable Micro Systems) [2]. Disintegration time of ODFs was analyzed using a modified disintegration tester (PharmaTest) (n=6) [3].

Content uniformity

Content Uniformity of ODFs was analyzed by HPLC (VWR). 10 ODFs were dissolved in 100 ml water and the content determined.

RESULTS: 3D-printing of ODFs with different infill design was feasible. ODFs are flexible and can be handled without breaking. One layered ODFs have a higher mass whereas two layered ODFs are thicker as expected. One layered ODFs show a higher force and therefore a higher puncture strength compared to two layered ODFs. Two layered ODFs show a faster disintegration because of their structure. In both cases the ODFs disintegrate within 30 sec and can be classified as orodispersible. Drug load of more than 30 mg for both ODF designs could be easily achieved.

CONCLUSION: Production of ODFs using 3D printing with a high drug loaded was feasible and provides a suitable method for the production of individiualized batches.

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OP-3

3D floating tablets: appropriate 3D design from the perspective of different in vitro dissolution testing methodologies

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INTRODUCTION: Gastro-retentive drug delivery systems (GRDDS) are acknowledged to increase the success rate of the oral administration route, however due to production difficulties and quality control-biorelevance inconsistencies only a few products have made their way on to the pharmaceutical market [1]. Three dimensional printing (3DP), a representative of the FDA's emerging technologies program, is set to modernize pharmaceutical manufacturing by simplifying the technological flow as to give better control over the process. Fused deposition modelling (FDM), represents a cost-effective 3DP technique that enables the simple production of porous structures, which may present floating capabilities [2]. The study proposed to develop carvedilol loaded 3DP floating tablets with the concomitant evaluation of the critical design features that are set to assure robustness to the final dosage form.

MATERIALS AND METHODS: Carvedilol, molecule with absorption window within the upper intestinal region, was incorporated into a polymeric matrix via hot melt extrusion (HME) (Haake Minilab, Thermo Fisher Scientific, USA) and printed into a porous structure via FDM (Craftbot Plus, Craftunique, Hungary). Design features (infill, shell structure, layer height) were submitted for evaluation. Dissolution kinetics and structural integrity was assessed from three separate dissolution test perspectives: one recommended by dissolution apparatus suppliers, one simulating simple in vivo floatability and one dissolution stress test.

RESULTS: Results confirmed that robustness is dependent upon structural integrity. Floating capabilities are governed by infill, while structural integrity is influenced by layer height and shell structure. The 3DP tablets presented instant floatation, with low dose dumping risks and dissolution kinetics with controlled release potential.

CONCLUSION: High floating capability dosage forms could be obtained by HME+FDM, serving as alternative, extended release delivery systems for carvedilol as opposed to Coreg CR. The dissolution tests showed different outcomes, proving that for in vivo relevance the formulation

and quality control for floating systems should be carefully considered.

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OP-4

Design of experiment (DOE) based methodology for designing polymeric NPs encapsulating Liraglutide for oral delivery

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INTRODUCTION: Liraglutide, a fatty acid modified glucagon like peptide-1 (GLP1) analog, with 97% amino acid sequence similarity to native GLP-1. This peptide drug was approved as a powerful treatment for type 2 diabetes mellitus in addition to chronic overweight management. Since this API is still administered parenterally, considerable effort must be devoted toward development of an oral delivery system from this drug. This work aims to design Lira encapsulated in polymeric nanoparticles for oral administration implementing DOE based strategy within the QbD framework.

MATERIALS AND METHODS: Liraglutide was loaded in PLGA nanoparticles by means of double emulsion solvent evaporation method and freeze-dried using lyoprotectans for further investigatons. This study evaluted the effect of PLGA amount, liraglutide theoritical loading, PVA concentration, 2nd step sonication time, lyoprotectant type and concentration in addition to external aqueous phase to organic phase w2/o ratio on the mean particle size of the prepared NPs. For this purpose; a 7-factor 2-level 8-run Plackett Burman design was applied using STATISTICA software, and analysis of variance (ANOVA) was applied to determine the statistical significance of each model coefficient, which was significant at 95% level ($P < 0.05$).

RESULTS: Statistical analysis of the obtained results revealed that all the examined parameters have a significant effect on the Z-average of the prepared NPs, while the selected levels of theoritcal drug loading have only a fuzzy effect on it. Moreover; the highest influential parameters affecting the mean particle size are the stabilizer and polymer levels.

CONCLUSION: Plackett Burman screening DOE was sucessfully implemented to understand the effect of CPPs and CMAs on the size of Liraglutide loaded PLGA NPs with limited number of runs.

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OP-5

Probiotic encapsulation technologies to protect and deliver microorganisms to specific target location

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INTRODUCTION: Probiotics can prevent or treat several diseases by shaping the local microbiota or by interaction with host cells. To have beneficial health effects they must be delivered in viable state. The challenge is what delivery system to use for probiotic bacteria that would promote their prolonged survival, efficient revival and successful colonisation of the target location.

MATERIALS AND METHODS: Two different delivery systems were investigated; [1] Ca-alginate microcapsules produced by prilling followed by the lyophilisation and [2] polymer nanofibers produced by electrospinning that led to the dry end product. Both delivery systems were thoroughly characterized from physico-chemical and biological viewpoint, focusing on the use of state-of-the-art microscopies, e.g. scanning electron microscopy (SEM), stimulated emission depletion (STED) microscopy, time-lapse optical microscopy.

RESULTS: With probiotic microencapsulation 120 - 150 μm sized microcapsules were produced, with positive or negative zeta potential (depending on the additional chitosan coating). Up to 1×10^8 (vegetative form) or 1×10^10 (spore form) of colony forming units per gram of dry microcapsules was encapsulated. Alginate matrix was sufficient for bacteria entrapment, allowed the inward diffusion of nutrients and oxygen, and was simply

disentangled to enable fast cell release. Surprisingly, already nanometer thin chitosan layer, represented a barrier, which enabled also sustained release of bacteria [1]. The electrospinning process is a good alternative to microencapsulation since it is only one step process and is usually having really high encapsulation yield of spores; up to 1×10^12 of colony forming units per gram of nanofibers. Again, with the different formulation composition (different polymers and ratios) the probiotic outgrowth and release could be modified [2].

CONCLUSION: Both, microcapsules and nanofibers, proved to be useful for the purpose of probiotic local delivery, with some distinct properties that can be exploited to finely tune the probiotic survival and release.

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OP-6

Solid formulation of living Clostridium butyricum by electrospinning

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INTRODUCTION: It has been shown that the gut microbiota plays a key role in human health and disease. Therefore, the interest in microbiome-based therapeutics has surged in the recent years [1]. The growing therapeutic role of microbiome drugs requires the maintenance of viability of bacteria during long-term storage. This goal is preferably achieved through drying, resulting in new challenges to the solid formulation technologists due to the sensitive nature of microbiome-based drugs.

Electrospinning provides a gentle and fast dehydration besides being a continuous and low energy consumption process resulting in an economically viable drying process alternative to the most commonly used drying technologies, such as freeze-drying and spray drying [2]. In this research the applicability of electrospinning was investigated to produce bacteria-containing solid formulations for oral administration while preserving the activity of the microbiome-based drug.

MATERIALS AND METHODS: The electrospun material was prepared by high-speed electrospinning [3]. PVA, PEO and mannitol were used as matrix materials in the electrospinning solution. The morphology of the fibers was studied by scanning electron microscopy. A commensal bacterium, Clostridium butyricum was used as the model drug. The viability of the bacteria was evaluated by the colony forming units counting method.

RESULTS: Electrospinning of the model bacterium, Clostridium butyricum was successful. Survival of the bacteria after the drying process was more than 92%. The electrospun bacteria containing fibrous material was stored at different temperatures and the viability of the bacteria was evaluated periodically. The fibers contained $6.5x10^8$ CFU/g living bacteria after 1 month storage at 4 °C, which is a sufficient amount for a solid oral dosage form.

CONCLUSION: The present work shows that electrospinning is a capable drying method for producing stable solid formulation of microbiome-based drugs and is an alternative to freeze drying and spray drying.

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OP-7

Development of particles with double pH-dependant release of model compound for application of suspension via feeding tubes

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INTRODUCTION: Physiological condition of specific groups of patients, such as prematurely born children or critically ill people in the intensive care units, often demands usage of (naso)gastric tubes for drug administration, feeding or both [1]. Active substances sensitive to acidic hydrolysis (e.g. proton pump inhibitors) require delayed release of drug as well as stability of such delivery system prior to application. The objective of the

study is to develop a particulate delivery system which would allow application of 'ex tempore' prepared multiple dose oral suspension via feeding tubes. For this purpose pharmaceutical particles with two functional coatings are designed. Interior coating provides gastro-resistance, while the exterior coating prevents dissolution in neutral or slightly alkaline medium of suspension.

MATERIALS AND METHODS: Granules with model compound tartrazine were prepared via high shear granulation, while micro pellets and pellets via layering with tartrazine. Particles were then film coated in three successive stages using a Wurster process unit with a swirl generator. Interior coating (Eudragit® L 30 D-55) provided gastro-resistance, while the exterior coating (Kollicoat® Smartseal 30D) prevented dissolution in a neutral medium. Intermediate barrier coating consisted of HPMC. The functionality of applied coatings was assessed by dissolution testing.

RESULTS: The results revealed that coated granules and micro pellets deliver the required release profile in neutral (pH=7.2), acidic (pH=1.2) and finally in slightly acidic medium (pH=6.8). Demonstrated release profiles allow for up to two hour 'ex tempore' suspension handling prior to administration. Simple preparation of aqueous suspension out of coated particles and powdered polymers mixture is possible by usage of magnetic stirrer. Only suspension with coated granules demonstrated suitable uniformity of dose after repeated withdraws with syringe, while both granule and micro pellet based systems were successfully pushed through Ch 10 feeding tube.

CONSLUSION: The concept of dual pH dependant drug release profile of coated particles compatible with feeding tubes was confirmed.

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OP-8

Combination Products: Balancing Innovation and Regulatory Constraints

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INTRODUCTION: The modern concept of drug delivery systems partially overlaps with the emerging field of combination products (CPs). CPs are indeed complex products with a regulatory status and a wide market share. Different types of CPs are classified in the regulatory documents.

FIXED-DOSE COMBINATION (FDC) PRODUCTS are formulations combining two or more actives in certain respective fixed doses in a single dosage form.

DRUG-DEVICE OR DEVICE-DRG COMBINATION PRODUCTS (DDCP) typically include a medical device and a drug. DDCP might be considered the modern evolution of drug delivery systems whereas one component (device) is functional to the performance of the other (drug). Thus, CPs increasingly incorporate cutting edge, novel technologies that hold great promise for advancing patient care.

The aim of the presentation is to show how innovation can be implemented in CPs and to indicate a road map to pharmaceutical development while respecting regulatory constraints.

MATERIALS AND METHODS: 1st STEP: the regulatory frame of EU scenario will be considered [1-3].

2nd STEP: the formulation development of two new FDC products will be unrolled, revealing the strategies adopted. One is a multiple unit dosage form, the other a tablet based on an enabling dissolution technology. The innovative module assembling technology is also proposed for FDCs.

3rd STEP: two fully-integrated DDCs will be presented. One is an innovative powder inhaler and the other a solid dosage form incorporating an ingestible sensor to check adherence to therapy.

RESULTS: The unrolled examples of new FDC products a stepwise approach should be adopted, keeping the formulation as simple and flexible as possible. In the development of DDCPs, a holistic approach is needed to take into account the interplay of both components not to forget the final goal of improved therapy and risk/benefit ratio.

CONCLUSION: A scientifically based pharmaceutical development is crucial for the success of any product. In the case of DDCPs customized performance tests capable of controlling the quality attributes relevant to in vivo performance may be needed. Overall the regulatory compliance should be considered during the whole development process.

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OP-9

The transparency principle for pharmacopoeial reference standards

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INTRODUCTION: Regulatory bodies expect pharmaceutical companies to demonstrate traceability of the medicinal product content values to internationally recognised references, such as pharmacopoeial reference standards (PhRS), to guarantee comparability of measurement results both over time and between laboratories, which can only be done if the uncertainty of the assigned value is known [1-3]. However, the uncertainties of the assigned values for PhRS are normally not stated. Moreover, the use of PhRS is typically limited to assessing compliance of medicinal products with pharmacopoeial specifications, which creates difficulties for users in providing analytical support for non-pharmacopoeial applications, such as pharmaceutical development, quality monitoring, using "guard bands" narrower than pharmacopoeial, certifying secondary reference standards for in-house use, and so on. Therefore, the need for developing the concept of certification and use of PhRS suitable for quality control tasks that are outside the pharmacopoeial monographs in compliance with contemporary regulatory requirements is apparent.

MATERIALS AND METHODS: Mathematical statistics, pharmacopoeial assays and purity tests.

RESULTS AND DISCUSSION: The transparency principle for PhRS was formulated. Based on the intended use, the values of target measurement uncertainty (MU_{target}) were set for the main pharmacopoeial tests. For PhRS intended for quantitative tests, the expanded measurement uncertainty of certified value (MU_{max}) should not exceed 0.32 of MU_{target} (i.e. should be negligible). The certificate of PhRS should contain the intended use of PhRS (tests, the narrowest content limits for assays, analytical methods); MU_{max} and the method used for evaluating the actual value of MU; the minimum sample weight for which the homogeneity of PhRS was confirmed (if necessary). Using the transparency principle, the State Pharmacopoeia of Ukraine (SPhU) has certified about 800 PhRS. The metrological base of certification and use of reference standards of SPhU is described in the General Text 5.12N "Reference Standards" of SPhU.

CONCLUSION: The set of properties of PhRS should ensure the correctness of their use outside pharmacopoeial monographs by regulatory requirements. Users should be informed about the suitability of PhRS for their tasks.

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OP-10

The application of artificial neural networks for the development of topical flurbiprofen microemulsions

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INTRODUCTION: Microemulsions are colloidal nano-carriers and their use as topical delivery systems derives from their multiple advantages compared to other dermatological formulations, such as ease of preparation, thermodynamic stability and penetration enhancing features [1]. In order to simplify the formulation of microemulsion-based colloidal drug carriers, there is a growing interest of researchers for the development of artificial neural network (ANN) models to predict and optimize the phase behavior of microemulsion systems using limited number of experiments and inputs [2, 3].

This study aims to develop flurbiprofen (FLB) loaded topical microemulsions by creating ANN combined with Genetic Expression Programming (GEP) and to investigate the skin penetration of FLB from the optimized microemulsions in comparison with the commercial topical product of the drug.

MATERIALS AND METHODS: The Critical Quality Attributes (CQAs) were microemulsion droplet size, pH, conductivity, refractive index, viscosity, and FLB skin deposition. Critical Formulation Parameters (CFPs) were oil, surfactant/co-surfactant (SAA/CoS), and water percentages. The commercially available INForm V5.1 ANN (Intelligensys, UK) was used to optimize the generated data.

RESULTS: The obtained results show that optimized ANN in combination with GEP may limit the experimental effort for the formulation of pharmaceutically acceptable microemulsion vehicles of FLB. In addition, the in vitro skin deposition of FLB from the optimized microemulsions was up to 5,9 fold higher when compared to the commercial gel formulation.

CONCLUSION: The ANN enhanced with GEP could be accepted as an effective tool to reduce research time and development cost for characterizing microemulsion properties. The ANN optimized microemulsions improved the skin penetration of FLB and hence could be useful alternatives to its conventional topical products.

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OP-11

Our experiences with freeze-dried fecal supernatant capsules in Clostridium difficile infection

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INTRODUCTION: Clostridium difficile infection (CDI) is widely known as a consequence of the broad-spectrum antibiotic use. Treatment attempts by antibiotics are getting less effective, as more and more cases are found to be resistant to the therapy, or recurring.

Our first and second line drugs both have major drawbacks: metronidazol has a decreasing success rate and by now it is evident that the use of vancomycin facilitates the spreading of vancomycin resistant Enterococcus fecalis/faecium (VRE). Fidaxomicin is known for its decent results in the treatment of CDI. Fecal microbiota transplant (FMT) has similar success rate to fidaxomicin, although several factors make this method circumstantial. We think that a reliable and more tolerable formulation of FMT could facilitate the use of the method and could also simplify the way to other perspectives.

MATERIALS AND METHODS: We administered soft gelatin capsules to CDI patients, filled with freeze-dried fecal supernatant. The stool was received from healthy donors. We also conducted metagenomic analysis of the stool of the donor and the recipients to determine the shifts in the gut microbiota after the treatment.

RESULTS: Our patients found this way of administration much more convenient and acceptable than our former method, the nasogastric tube. We found the success rate non-inferior to our former attempts with nasogastric tube. The metagenomic analysis showed significant changes in the composition of the gut microbiota. The final results will be discussed in the presentation.

CONCLUSION: Based on our observations, we think that using freeze-dried fecal supernatant capsules in Clostridium difficile infection is a promising field of research. We recently noticed a decrease in the number of our new CDI patients, therefore it is difficult to find an appropriate number of cases for our further investigations.

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OP-12

Antimicriobial and cytotoxic interactions between different pharmaceutical excipients in liquid preparations

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INTRODUCTION: Preservatives are the essential part of any orally administered liquid pharmaceutical product as a solution, suspension, emulsion or syrup. However, these chemicals are cheap and considered to be relatively safe, recent publications question the way we use them. Either the insufficient antimicrobial protection [1], or the new toxic effects [2] highlight that the traditional preservative policy must be reconsidered. The aim of our research is to discover new antimicrobial and cytotoxic interactions between different components of a liquid formulation. The different solutions of preservatives, surfactants and solvents are mixed and systematically tested to screen for any occurring positive or negative effect.

MATERIALS AND METHODS: We planned two independent experiment to find interaction between different pharmaceutical excipients. In the first, we formulated to complex co-solvent systems with a co-solvent and a surfactant in each, adding equal concentrations of parabens (methyl, ethyl, propyl, butyl) into both. At the second, we tested sorbates, benzoates, propionates (acidic form, sodium, potassium, calcium salt) at different pH values (pure solution in water, adding HCl or NaOH). In case of both experiments cytotoxicity and antimicrobial properties were detected. We measured cytotoxicity with a colorimetric cell-viability assay, the MTT-test and the time-dependent toxicity with a real time cell electronic sensing device. Caco-2 human adenocarcinomal cells were used for a representation of the gastro-intestinal tract. The inhibitory effects of the different solutions were measured on C. albicans, C. glabrata, C. parapsilosis and E. coli, P. aureginosa, S. aureus with simple microdilution method.

RESULTS: The two complex co-solvents systems could change the relative toxicity of parabens on human cells and in certain cases they could greatly enhance or slightly reduce the antimicrobial properties of these esters. The other group of preservatives showed pH dependency in case of toxicity and inhibitory activity and even paradoxical effect could be detected.

CONSLUSION: Finding the positive and avoiding the negative interactions between different pharmaceutical excipients are a key to lower the required amount of total excipients, thus increase microbial stability and decrease toxicity.

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OP-13

The impact of supercritical drying of microcrystalline cellulose on its tableting characteristics

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INTRODUCTION: Due to its outstanding dry binding properties, microcrystalline cellulose (MCC) is one of the most important tableting excipients, that enables the manufacture of tablets by direct compression [1]. It is commonly manufactured by spray drying of the neutralized aqueous slurry resulting from the treating α - cellulose from plant material with mineral acids [2]. Present work was aimed to investigate the effect of supercritical drying of the MCC on its tableting properties.

MATERIALS AND METHODS: Wheat straws were milled, purified with hexane and methanol, followed by processes of delignification and bleaching by using NaOH and $NaClO_2$. Bleached cellulose pulp was hydrolyzed with sulphuric acid. A semi-continuous drying process was carried out in the Autoclave Engineers SCE Screening System, using supercritical CO_2 (20 MPa, 40 °C). Dynamic powder compaction analyzer (Gamlen Tableting Ltd., UK) was used to tablet samples and measure their tableting properties. The results were compared with commercial MCC (Vivapur®, PH101, JRS Pharma, USA).

RESULTS: The neto compression work, ejection stress and tablet tensile strength of the MCC samples were measured and compared. The results indicated that MCC derived from wheat straw has similar neto compression work (0.42±0.005 – 1.17±0.001 N*m) to Vivapur® (0.30±0.003 – 1.07±0.02 N*m). Therefore, we can assume that both have good compressibility. In addition, no significant differences in tensile strength and ejection stress of the tablets prepared from all the samples were evidenced.

CONCLUSION: A similar compressibility, compactability and manufacturability of all the MCC samples, which are obtained from wheat straw and dried using supercritical CO_2 to Vivapur® was demonstrated. Accordingly, it can be concluded that supercritical drying has no negative impact on tableting properties of the wheat derived MCC samples. Moreover, it represents a good alternative to spray drying method used for the commercial MCC.

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OP-14

Processing of amorphous solid dispersions containing itraconazole

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INTRODUCTION: Electrostatic spinning is a promising technology in the production of amorphous solid dispersions (ASDs). The high surface area of the electrospun nanofibers and the fact that the drug is in amorphous form both contribute to the increased dissolution achieved by ASDs. The aim of the current study is to produce tablets containing an ASD of itraconazole, a systemic antifungal drug and two different matrix polymers, hydroxypropyl methylcellulose (HPMC) or vinylpyrrolidone-vinyl acetate copolymer (PVPVA).

MATERIALS AND METHODS: HPMC 2910 or PVPVA 64 was used as matrix polymer. ASDs were produced using the high speed electrospinning method [1]. Before compression into tablets, ASDs were processed using various methods, including hammer milling, oscillatory milling, pressing through a sieve and roller compaction. Tablets were compressed on a single punch tablet press equipped with 14 mm concave punches. In vitro dissolution measurements were carried out in pH 1.2 HCl solution on a Pharmatest PTWS600 dissolution apparatus.

RESULTS: It was observed that magnesium stearate, the lubricant used in the tablets deteriorates dissolution when PVPVA is used as matrix polymer, while HPMC can prevent this phenomenon [2]. On the other hand, compression into tablets is more feasible in the case of PVPVA. Therefore several formulations were developed which combine the benefits of the two matrix polymers by adding various forms of HPMC to PVPVA-based ASDs. These include using HPMC as excipient, as film coating of the tablets and a new ASD which uses both polymers as matrix in a 2:1 PVPVA to HPMC ratio. These formulations significantly improved dissolution compared to the case where only PVPVA is present. An effort was also made to improve the processability of HPMC-based ASDs by applying roller compaction to the electrospun material.

CONCLUSION: In order to produce an appropriate tablet formulation, we either need to utilize the benefits of both matrix polymers or to significantly improve the processability of HPMC-based ASDs.

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OP-15

"One for All - All for One": simultaneous control of polymorph outcome and particle engineering of caffeine-anthranilic-acid cocrystal through polymer-assisted grinding

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INTRODUCTION: Cocrystallization technology is gaining popularity especially in the formation of new materials as well as providing an opportunity to synthesise organic solids by design [1]. On the other hand, polymer-assisted grinding (POLAG) is demonstrated to provide a new class of catalysts for improving reaction rate and increasing product diversity during solid-state cocrystallization reactions [2]. Here, we propose the use of POLAG for the simultaneous control of product polymorphic form and powder particle characteristics during mechanochemical cocrystal formation.

MATERIALS AND METHODS: We selected the caffeine-anthranilic acid as a model cocrystal since it has been previously explored for the production of different polymorphic forms [3]. Different polyethylene glycol (PEG) polymers (liquids and solids) with molecular weight from 200 to 20,000 were selected as catalysts for POLAG. PEGs find a wide range of applications both in the chemical and pharmaceutical industries. All the materials were purchased from Sigma-Aldrich Company, Ltd. (UK) and used without any further purification.

RESULTS: The results suggested that low amounts of long chain PEGs promote the formation of the metastable polymorph Form III, while PEGs with a shorter chain length produced co-

crystal Form II. Form I depended on the amount of the polymer used. The powder particle size was equally correlated to both the amount of the polymer used and polymer chain length.

CONCLUSION: By varying the amount of the polymers employed to the solid reactants as well as modifying the number of monomer units, it was possible to access to all the known polymorphic forms of the model system selected in this study. Additionally, it was possible controlling the powder particle characteristics of the finished products.

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OP-16

Impact of particle morphology and multi-scale hierarchical structures on tabletability

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INTRODUCTION: Tabletability describes the relation between compression pressure and tensile strength of tablets. Tabletability differs highly between different types of material. However, tabletability can vary widely even for the same type of material depending on the morphology of the starting material and/or an intermediate granulation process. The multi-scale hierarchical structure (primary particle, agglomerate, granule, tablet) of starting materials, intermediate granules and final tablets has been discussed in [1]. Pores can be present on each scale, which can affect the mechanical properties of a material. The purpose of the study is to find common patterns in starting material properties, which are relevant for its tabletability.

MATERIALS AND METHODS: Different types of dibasic calcium phosphate [1], calcium carbonate [2], lactose [3] and isomalt [4] were compressed to tablets directly or after roll compaction/ dry granulation. The starting materials were characterized by particle size distribution, specific surface area and particle density. Tensile strength and porosity of tablets were measured.

RESULTS: For all tested materials the tabletability depended on the morphology of the starting materials. Highly functionalized excipients like Fujicalin or Omyapharm 500-OG resulted in high tabletability. Although dibasic calcium phosphate and calcium carbonate are known as brittle materials, the functionalized qualities resulted in tablet behavior like more plastic materials after roll compaction. By studying the properties of the intermediate ribbons and granules, this behavior can be explained.

CONCLUSION: Not only the chemical type of a material, but also the physical morphology of the particles influences its tabletability. This opens new perspectives for a tailored particle design.

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OP-17

Near Infra-Red spectroscopy for content uniformity of powder blends- focus on calibration set development, orthogonality transfer and robustness testing

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INTRODUCTION: NIR spectroscopy is frequently applied in pharmaceutical field, ranging applications from raw material identification to in-line process monitoring, however its efficient application relies on the method development phase [1, 2]. The objective of this work was to develop and validate a NIR method for the quantification of three active ingredients from powder blends, followed by the evaluation of method's robustness to factors not included in the calibration.

MATERIALS AND METHODS: Calibration set was built based on a D-optimal experimental design with three factors (ibuprofen, paracetamol, caffeine) and five variation levels (80-90-100-110-120%), ensuring orthogonal variation between ingredient concentration. Prior to model development the effect of pre-processing method was assessed by decomposing spectral varibility into predictive and orthogonal parts. Robustness of the method to different active ingredient suppliers and relative humidity was tested following a DOE approach.

RESULTS: Comparing the distribution of formulations in spectral vs concentration space aided the selection of an appropriate pre-processing method and highlighted concentration combinations with biased predictions. NIR method was validated on the full calibration range using ± 5% acceptability limits for paracetamol/ibuprofen, and ± 10% limits for caffeine. Robustness testing results showed that the accuracy of caffeine content predictions was influenced by relative humidity, while paracetamol/ibuprofen predictions were robust to all factors.

CONCLUSION: Redefinition of interfering factor variation level was beneficial to reduce the bias in caffeine content predictions making the method suitable for routine use.

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OP-18

Non-destructive spectroscopic analysis and artificial intelligence for dissolution prediction of pharmaceutical tablets

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INTRODUCTION: By the advent of continuous manufacturing, the need for fast and accurate characterization of product quality has become a major interest. Utilizing a combination of process controls and in-process measurements, real-time release testing (RTRT) systems can be established, which provide assurance that the product is of intended quality based on process data, product and process understanding and control [1]. This work introduces the application of NIR and Raman spectroscopy and artificial neural networks to serve as a surrogate for destructive dissolution prediction and analyze crushing strength and friability.

MATERIALS AND METHODS: The applicability of Raman and NIR spectroscopy to predict tablet properties were tested in two different model systems, namely a three-component immediate release tablet manufactured in a continuous powder blending and tableting line and in four-component extended-release tablets. Design of experiment approach was applied to fit response surfaces to characterize the influence of critical quality attributes (e.g. tableting pressure, lubrication properties, constitution of the tablets) on tablet properties. Then, Raman and NIR spectra were measured and chemometric models and neural networks were developed to establish predictive relationships between the spectra and the dissolution, crushing strength and friability of the tablets.

RESULTS: The developed spectroscopic methods were applicable to non-destructively characterize lubrication properties, e.g. reveal overlubrication in the continuous manufacturing line as well as predict dissolution of extended-release tablets, solely based on the measured vibrational spectra.

CONCLUSIONS: Our study demonstrated that Raman and NIR spectroscopy can complement each other and effectively contribute to the prediction of tablet physical properties and dissolution in a fast and non-destructive manner. Consequently, by extending it to further manufacturing steps and coupled with adequate control, they can be effective tools for RTRT strategies.

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OP-19

Polymeric patches as a drug carrier for dermal delivery of dexamethasone and voriconazole – the effects of physicochemical and structural properties of the patch on the adhesiveness

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INTRODUCTION: In traditional semi-solid formulations, only limited amount of drug substance applied on the skin is delivered to the target site e.g. due to vehicle removal. Patch as a drug carrier provides sustained drug delivery with prolonged skin contact and improved compliance due to decreased dosing frequency [1]. Still, formulating a polymeric matrix that will retain good skin contact with no unwanted interaction with the drug remains a constant challenge [2]. Current project focused on the search for a matrix carrier for two model drugs, where physicochemical characteristics of polymer blends and film surface structure on the patch adhesiveness is examined.

MATERIALS AND METHODS: PDMS (polydimethylosiloxane, MG 7-9850, Dow Corning, USA) or copolymer of methyl methacrylate and ethyl acrylate (Evonic, Germany) with a plasticizer (ethylene citrate) were used as patch forming material. Polymer blends with dexamethasone or voriconazole (1% and 5% w/w) were prepared in planetary mixer (Thinky ARE-250, Japan) and formed into thin films (200 μm - 500 μm) by casting. Fluorescence microscopy and SEM were used for imaging of the films structure, whereas atomic force microscopy (AFM) provided detailed topographical information. Additionally, a two level full factorial design (2^3) was performed to estimate the effect of formulation physicochemical parameters (composition, thickness and roughness) on the patch adhesiveness, assessed by tack test and 90° peel test (texture analyser TA.XT Plus, UK).

RESULTS AND DISCUSSION: Voriconazole showed incompatibility with PDMS. Both polyacrylic and PDMS patches with dexamethasone exhibited homogenous structure with sufficient adhesiveness. AFM imaging revealed films' diverse surface structure, which was found weakly related to the adhesiveness. Results also showed that high content of a plasticiser affected the adhesiveness considerably more than the film thickness.

CONCLUSIONS: Multifactorial approach allowed to preliminary identify properties of the patches, which impact patch adhesiveness. This work contributes to the design and optimisation of polymeric dermal patches.

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OP-20

Effect of different glidant types on flow properties of pharmaceutical excipients – A comparison of Neusilin® and Aerosil®

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INTRODUCTION: Flow properties are one of the most important characteristics of pharmaceutical powder blends due to their influence on the content and weight uniformity of the final product – tablets or capsules. In order to improve flowability of powders, flow enhancers or glidants are widely incorporated in solid dosage forms [1]. Traditional glidants, such as colloidal silica (e.g. Aerosil®), are surface-active particles and their action is very sensitive to formulation and process parameters of the mixing operation [2]. The work was aimed at comparing mechanism of improving excipient flow properties using novel family of glidants - magnesium aluminosilicate materials (commercially available e.g. as Neusilin®) to Aerosil®.

MATERIALS AND METHODS: Several blends comprising the model excipient and model glidants were prepared and their flow properties were characterized using a powder rheometer FT4 (Freemantech, UK). The blends were formulated to represent the effects of particle size, glidant loading, and mixing time. After pre-conditioning, the flow properties were measured using shear test, compressibility, and flow energy measurements.

RESULTS: Unlike Aerosil®, the mixtures incorporating Neusilin® exhibited proportional improvement of flow properties without any maxima. Therefore, there is no risk of glidant overloading for those excipients. Moreover, it was found that Neusilin® retains its negative cohesion values even in the mixture with other compounds, i.e. Neusilin® particles tend to separate from each other and hence, no need of glidant de-

aggregation was required. As a result, the equilibrium of flow properties was reached in the mixtures containing Neusilin® only after a short mixing time.

CONCLUSIONS: The mechanism of Neusilin® action was found to be different compared to Aerosil®, having less process sensitivity, so that Neusilin® utilization as glidant could be advantageous for the formulation performance.

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OP-21

Pulsed laser ablation in liquid (PLAL) as a suitable particle engineering technique to modify the physicochemical properties of meloxicam

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INTRODUCTION: Pulsed laser ablation in liquid (PLAL) could offer a new challenge in the field of pharmaceutical technology by controlled fabrication of micro- and nanoparticles. PLAL is therefore a non-conventional approach in drug formulation as a simple and fast wet grinding method (1). The motivation of this work was to introduce the effect of PLAL technique (with different laser fluence (4.2-9.4 J cm^{-2}) and stabilizer (Polyvinyl alcohol (PVA)) concentration 0; 0.5; 5 w/w%) on the size decreasing of drug therefore to modify its physicochemical properties.

MATERIALS AND METHODS: A poorly watersoluble drug, meloxicam (Egis Plc., Hungary) was used as model drug. Polyvinyl alcohol 3-88 (PVA) was purchased from ISP Customer service GmbH, Germany.

A frequency doubled Q-switched Nd:YAG laser beam (Model: G-NY, GBL Optic-Electronic CO., Ltd, λ=532 nm, FWHM=8ns) was used by varied laser fluences using meloxicam pastilles placed in 20 ml of aqueous solution. Morphology and size of the generated meloxicam particles were determined by Scanning Electron Microscopy (SEM) image analysis. Moreover, their structure (XRD, FTIR and DSC), solubility and dissolution were also investigated.

RESULTS: Morphological investigation showed that the main parameters of the produced suspension contained particles between 0.1 μm -10 μm depend on the laser fluence and PVA content. According to the structural characterization of the prepared samples chemically identical with the raw drug was observed, however with the presence of PVA the crystalline structure of meloxicam was turned to amorphous form which also improved its dissolution rate.

CONCLUSION: Based on our results we can concluded, that PLAL process is suitable for production of micro- and nanoparticles as superior intermediate product to develop traditional and innovative drug formulation.

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Posters

P1- DERMAL AND TRANSDERMAL DELIVERY 1.

P1/1

Development and Characterization of Fusidic Acid Loaded Thermosensitive In Situ Gels

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INTRODUCTION: Burn wound is one of the painful physical injuries and it has very complex treatment procedure [1]. Fusidic acid (FA), which is an antimicrobial agent with a special working mechanism, is used for the treatment of burn wound [2]. In situ gel systems are liquid aqueous solutions at room temperature and they have the ability of converting their liquid aqueous phase into gel form once they administered to the related physiological area [3]. The aim of the present study is to formulate and evaluate FA loaded topical in situ gels in order to be used in the treatment of burn wound.

MATERIALS AND METHODS: Poloxamer 407, Poloxamer 188 and Poloxamer 338 were used as polymers for preparation of in situ gels. In situ gels were prepared by using the cold method [3]. The formulations were prepared by completely dissolving the different concentrations of poloxamers in water. Different concentrations of poloxamers, FA (2%), alcohol (5%) and distilled water (qs.100) are the components of formulations. For characterization and evaluation of the in situ gels, gelling temperature, pH, clarity, gelation capacity, spreadability, drug content, rheology parameters of prepared formulations were measured.

RESULTS: As result of the preformulation studies, the gelling temperatures of the formulations were determined in between 26.4±0.1-47.3±0.1°C. Characterization studies of the ideal formulations showed that the gelling temperature of the formulations were in between 31.36±0.66-32.46±0,21°C. This indicates that the formulations can convert their structure into the gel when they are administered to the skin surface. The pH of the formulations ranged between 5.7±0.07 and 6.05±0.1. All the formulations showed fair uniformity of drug content which ensures adequacy of the method of the in situ gel preparation. The rheology values of formulations were varying from 99.43±0.75 to 175.33±0.05 cP. Results of clarity and gelling capacities parameters of the developed formulations were acceptable.

CONSLUSION: The present study showed that FA loaded in situ gels can successfully be prepared with cold method. In conclusion, this study showed that developed in situ gel formulations could be alternatively used as topical delivery of FA for the treatment of burn wound.

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P1/2

Evaluation of Emulsion Forms via Quality by Design (Qbd) Approach

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INTRODUCTION: For a long time, drug delivery through the skin has been a favorable concept [1]. In this study diclofenac sodium has been used as an active pharmaceutical ingredient. The aim of the study was to ensure the product has desired quality attributes during the development of semisolid topical product after implementing QbD approach.

MATERIALS AND METHODS: Materials: Diclofenac, EDTA, Carbopol 940, Triethanolamine, Tween 80, Span 20, Ethanol, Propylene glycol, Liquid Paraffin, Oleic Acid.

Methods: The hydrogel of emulsion gel was prepared by dispersing Carbopol 940 in purified water.

EDTA, Triethanolamine, and Tween80 was added. The oil phase was prepared by span 20, Ethanol, Propylene Glycol, with Liquid Paraffin in some formulation and Oleic Acid in other. Diclofenac sodium was dissolved in oil phase. Both oil phase and hydrogel were separately heated to 70 to 80 °C then the oil phase was added to hydrogel with continuous stirring until it cooled to room temperature 25 °C (2). After that optimized formulation was prepared with the help of artificial neural network (ANN) program by using the same method.

RESULTS: The mean Diameter (μm) of the formulations are ranged from 0,700 to 2,085 and the SD of the formulations are ranged from 0,20 to 0,91. The pH values of the formulations ranged from 5.9 to 7.1 and the Electrical Conductivity values ranged from 20 to 210 μS^{-1}. The viscosity values (Maps) of the formulations are ranged from 130 to 5250. Optimized formula was prepared and tested. Viscosity of formula is 4600, pH value is 6.7, electrical conductivity is 120 μS^{-1}, and particle diameter is 0,989 μm.

CONSLUSION: Preformulation were preformed, the next step of the study to evaluate the datas with the help of ANN program and to find optimum formulation composition. The optimal formulation was found and prepared. The results were ideal. Although, the artificial intelligence programs are not enough to build and develop formulations by itself, but they play a good rule in the formulation developing.

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P1/3

DSC compatibility study in binary physical mixtures of adapalene, levofloxacin, meloxicam, and miconazole

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INTRODUCTION: Transdermal therapeutic systems (TTSs) are innovative pharmaceutical forms and can be formulated for local or systemic effect [1]. In our study, we analyzed the physicochemical compatibility between four candidate drugs to be included in a TTS device. Thermal stability of free compounds and binary mixtures of adapalene (ADP), levofloxacin (LVF), meloxicam (MLX), and miconazole (MCZ) was analyzed by Differential Scanning Calorimetry (DSC) [2].

MATERIALS AND METHODS: ADP, LVF, and MCZ were purchased from Sigma Aldrich (Germany), and MLX from Techno Drugs & Intermediates Ltd. Mumbai (India). Thermal behavior of free drugs and binary mixtures (1:1) was evaluated using a DSC 60 Shimadzu device, 3 mg samples (weighed in crucibles of aluminum) with 20 °C/min heating rate. The melting points of the four compounds and six mixture, the stability and possible interactions between drugs were evaluated.

RESULTS: DSC curves of the binary mixtures showed changes in the melting point values of free drugs, dehydration, and some chemical interactions. Dehydration was observed mainly in the case of LVF [3], and some endothermic changes with peaks characterized by lower intensities and shift to lower temperature values in case of ADP-MLX. Exothermic events occur probably due to the formation of hydrogen bonds between two carboxyl groups or between chlorine atoms and hydroxyl/carboxyl group (ADP-LVF, LVF-MCZ, and MCZ-MLX). Moreover, dipole forces may occur between fluorine-carbon and chlorine-carbon bonds or between fluorine/chlorine-carbon and the hydroxyl-carbon bonds of MLX (LVF-MCZ and LVF-MLX). Possible changes such as a decarboxylation process (LVF-ADP), a chemical interaction between the carboxyl and secondary amine groups (LVF-MLX), and sample decomposition (ADP-LVF and LVF-MCZ) were also highlighted.

CONCLUSIONS: Modifications of DSC curves of all mixtures occurs over 175°C. The fewest and minor changes on DSC curves are observed in case of ADP-MCZ and ADP-MLX mixtures; these two blends can be considered as potential candidates for future TTS binary formulations. Also, others compatibility studies need to be performed.

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P1/4

DSC evaluation of ethylcellulose as dispersion modulator for including oxicams in hypromellose matrices developed for dermal use

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INTRODUCTION: Hypromellose (HPMC) forms water-soluble bioadhesive films by evaporating the water from its aqueous dispersions. The methyl substituent is hydrophobic while the hydroxypropyl is relatively hydrophilic [1]. Addition of ethylcellulose (EC), hydrophobic polymer, may modify the HPMC solubility and consequently the cohesive strength achieved when oxicams (4-hydroxy-1,2-benzothiazine carboxamides, practically insoluble in water [2]) are included in this kind of matrices. This study aims the evaluation of meloxicam (MX) vs. tenoxicam (TX) included in two types of HPMC (-EC) matrices.

MATERIALS AND METHODS: Ten products in the form of polymeric films containing 4% MX or TX were subjected to differential scanning calorimetry (Shimadzu TA-60WS, samples of 5mg, heating rate of 5°C•min^{-1}, range of 30-300 °C). Their compositional differences were coded as follows: P1 -low viscosity HPMC (24% polymer in matrix), P2 -high viscosity HPMC (8%), P3 -EC (8%); P1-P3 and P2-P3 based on HPMC+EC (24% + 8%).

RESULTS: All MX matrices showed characteristic DSC curves with endothermic peaks given by the melting point of MX. The reduction in enthalpy suggested the minimization of MX recrystallization, but also the non-homogeneity in the matrix. These types of findings were observed only for three TX matrices. The flatness of DSC curves registered for TX-P2-P3 and TX-P3 matrices suggested that EC favoured the dispersion of TX (by dissolution or amorphization of the crystalline powder) in the matrix based on HPMC of high viscosity.

CONCLUSIONS: EC can differentially modulate the grade of dispersions of oxicams (ingredients with low hydrophobicity differences) in matrix systems based on HPMC.

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P1/5

Development of bioactive compounds-loaded chitosan films using a QbD approach

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INTRODUCTION: In the present study, a Quality by Design (QbD) approach was applied in order to develop and optimise a bioactive compounds-loaded chitosan film formulation, intended for further use as an aid in the acceleration of diabetic wound healing.

MATERIALS AND METHODS: Chitosan was chosen as film forming polymer, polyethylene glycol (PEG) was used as plasticiser, while polyvinyl alcohol (PVA) was added to improve the film bioadhesive properties. A concentrated alcoholic extract consisting of a mixture of Plantago lanceolata, Arnica montana, Tagetes patula, Symphytum offcinale, Calendula officinalis and Geum urbanum was added in the formulation in order to enrich the film with bioactive compounds.

Risk assessment strategy was applied to identify the critical formulation variables. The factors that registered the highest scores were the chitosan concentration and the proportions of PEG and PVA, these being further introduced as inputs of a 3 level Box Behnken design of experiments (DoE). The studied outputs of the DoE were critical quality attributes of the films, namely: film thickness and transparency, swelling degree, solubility, bioadhesive and mechanical properties assessed through texture analysis.

Solutions consisting of chitosan, PEG, PVA and alcoholic extract, all in various proportions according to the DoE specifications, were prepared and casted onto polypropylene plates. The films were obtained after drying at 40°C for 24h.

Following experimental data analysis, the Design Space (DS) was established and an optimal formulation within the DS was prepared.

RESULTS: The antimicrobial effects of the optimised film formulation, as well as of a placebo formulation without bioactive compounds, against common wound pathogens such as S. aureus, E. coli and P. aeruginosa were determined by the disk diffusion method and subsequently compared.

The optimal film formulation obtained registered a film thickness of 0.092 mm, transparency of 1.52, solubility in water of 44.8% and a high swelling degree of 2157%, values within the specifications of the quality target product profile. Moreover, the optimal bioactive compounds-loaded chitosan film formulation was found to have a good antimicrobial activity against the tested pathogens.

CONCLUSION: Taking into consideration the promising results obtained, we can conclude that in the current study, the QbD approach was successfully applied in order to ensure a good understanding of the manufacturing process, as well as to optimise the formulation of chitosan films.

P1/6

Stability Testing Of Semisolid Individual Preparations Containing Cacao Butter

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INTRODUCTION: Pharmacy practice includes traditional and customized magistral products that are well-tolerated by patients, for which shelf-life time cannot be accurately provided. In such cases, the product may not meet the desired requirements even within the expiry date. This problem not only gives rise to uncertainty among patients and pharmacists, but is also of quality concern [1, 2]. Moreover, by carrying out certain examinations, even in the small-scale production, an appropriately stable pharmaceutical composition can be prepared.

The aim of this study is focused on the re-production of a routinely used individual preparation, its physico-chemical, accelerated and real-time stability testing to predict the rate of change at a proposed storage temperature.

MATERIALS AND METHODS: Five variations of the chosen ointment were freshly prepared and subjected to accelerated stability testing at 40°C; 75±5% relative humidity and 25°C; 40±5% relative humidity. The preparations were monitored and few units of the reference material were taken at 1, 3 and 6 months interval. During the stability testing process the following experiments and tests were conducted according to the Hungarian and European Pharmacopoeias: Drop point and freezing point measurements, extensometric test, microscopic examination, pH measurements of the watery phase, rheometric, dissolution and diffusion tests.

RESULTS: The study revealed that the choice of an optimal method of preparation results in a more stable pharmaceutical product than the original preparation. Even similar production methods resulted in ointments with significantly different physico-chemical parameters. Based on the study, we can recommend a good manufacturing practice, expiry date, packaging material and storage conditions regarding the chosen formulation.

CONSLUSION: These results confirmed that the physical and chemical stability of the ointments were achieved with the appropriate choice of the preparing conditions.

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P1/7

Formulation and Evaluation of Carvedilol Ointment

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INTRODUCTION: The aim of the present work was to study the preformulation parameters of

carvedilol ointment. The use of preformulation parameters maximizes the chances in formulation of acceptable, safe, efficient and stable product and at the same time provides the basis for optimization of the drug product quality. Calcium antagonists and beta-adrenergic receptors antagonists are known drugs, and for many years are widely used in the treatment of cardiovascular diseases. Some of these components also show antioxidant activity. For the purpose of testing potential local anti-inflammatory activity of beta blocker containing ointments, a 1% carvedilol ointment was prepared in the fatty carbohydrate medium. We demonstrated that a 1% carvedilol ointment has anti-inflammatory effect.

MATERIALS AND METHODS: For the purpose of testing the possible local antiinflammatory activity of ointments containing carvedilol the ointments with 1% of active substance in the oily base of the hydrocarbon were made. Particle size of carvedilol from manufacturer A, B, C and D was determined by laser diffraction using a PSA Instrumet: Malvern Master Sizer 2000 (PSA- Particle Size Analysis).

RESULTS: The mean particle size of carvedilol in different samples.

Particle size A B C D
d(0,1) 8,62 10,57 8,21 6,06
d(0,5) 24,27 47,58 23,34 24,77
d(0,9) 372,29 208,61 163,30 251,66

CONCLUSION: The histogram of particle size distribution of carvedilol indicated a wide particle size distribution, with sub micron particles in the field, and particles sized up to 1000 microns. Although for the product such as cream/ointment, narrower particle size distribution is recommended due to the uniformity of content, tests have shown satisfactory quality of ointments in which carvedilol was incorporated as the active substance. No data on the topical application of the beta blocker were found for the purpose pharmacological treatment of the reduction of the inflammation of the skin.

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P1/8

Carvedilol ointment stability

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INTRODUCTION: The aim of the present work was to study the stability of carvedilol ointment. Carvedilol is cardio selective beta blocker and has been used for the treatment of cardiovascular diseases for a number of years. It also shows antioxidative activity. The mechanism of antioxidative activity of carvedilol is unknown. For the purpose of testing potential local anti-inflammatory activity of beta blocker containing ointments, a 1% carvedilol ointment was prepared in the fatty carbohydrate medium. We demonstrated that a 1% carvedilol ointment has anti-inflammatory effect.

MATERIALS AND METHODS: A 1% ointment with carvedilol as the active substance was used in the project. Testing of the stability of the samples of finished ointments stored at 25°C 60% and the 40°C/75% was performed with two analytical methods: UV spectroscopy on 275 nm and high pressure chromatography adopted from BP 2009 monograph.

RESULTS: chemical evaluation of ointment stability at 25°C/60% and 40°C/75% RH conditions show that content of carvedilol was for 3 months 99,40%-102,50%, and for 6 months 98,50%-99,00%. Impurities was for25° C/60% RH for 3 months single 0,04%, total impurities 0,08%, for 6 months 0,03%, total impurities0,08%, and for 40°C/75% RH single 0,04% total impurites-0,08%, for 6 months single 0,03%, total impurities 0,08%,

CONCLUSION: By comparing the results obtained from these two methods no differences of the said content were observed. In the tested ointments the carvedilol content is within the limits prescribed for ointment monographs (95,00 to 105,00% in accelerated aging test as well as in normal ageing test at 25°C over a period of 6 months).

From the results of the study six months of stability carvedilol ointment at 25°C and testing (40°C), it can be concluded that carvedilol ointment is equal stable at both temperatures for 6 months. The samples stored according to ICH recommendations did not show significant degradation. Based on the obtained results, a shelf life of at least one year can be assigned according to the

ICH guideline recommendations for stability testing of the new forms.

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P1/9

Oscillatory rheometric detection and tracking of interactions between macrogol-phenolic compounds

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INTRODUCTION: Study of incompatibilities and interactions represents an outstanding field of the pharmaceutical technology. Incompatibilities manifesting in liquefaction can even prohibit the application of dosage forms such as suppositories. Observation of interactions between macrogol and hydroxil-group containing compounds can be followed by rheometer.

MATERIALS AND METHODS: The alterations of viscosity due to reaction between polyethylene glycol 6000 and phenol-group compounds such as salicylic acid (SA), phenyl-salicylate (PS) and vanillin (V) were measured using a Kinexus Pro oscillatory rheometer [Malvern Ltd.]. Oscillation tests were carried out to follow the changes of elastic and viscous moduli. Increasing amounts of active ingredients (0, 5, 10%) were added to a mixture composed of 7:3 PEG 6000: distilled water. Temperature-dependent oscillation measurements were performed while the samples were cooled from 60°C to 15°C and the reduction of congealing point was detected.

RESULTS: Oscillatory testing occuring between the polyethylene glycol 6000 and phenol-group compounds caused alterations in rheological properties. Samples containing 5; 10% of the active ingredient triggered incompatibility. Rheological modifications can be observed in alteration of complex viscosity and complex modulus dependent of temperature as well.

CONCLUSION: Measurements on an oscillatory rheometer can pinpoint incompatibilities manifesting in the fluctuation of viscosity.

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P1/10

Textural properties of matrix adhesive system containing plant extract

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INTRODUCTION: Transdermal patches have been useful in developing new applications for existing therapeutics by having several advantages [1]. This experimental study deals with formulation of a matrix system containing extract from Rhodiola rosea root (provided by Calendula, Slovakia). Studied polymer matrix system is aimed to be both, the reservoir and the controlling unit for transdermal plant extract delivery [2]. Adhesion as qualitative property of a transdermal patch is important in formulation process. We were focused on texture analysis with the aim to improve the physical characteristics of evaluated matrix system.

METHODS: Transdermal patches were prepared by using different polymers: 3% Carbopol, 5% pectin, 2% chitosan and combination of 13% gelatin and chitosan in concentrations 0.5%, 1%, 1.5%. The patches were prepared by casting into the form with standard area as a film with thickness of 1mm. The size of the film was standard (30mm x 30mm) with the dose of extract 60mg. Adhesion of evaluated polymer matrices we measured in two steps. In the first step adhesion was described by the force or weight needed for separation of two jaws connected through the polymer matrix by using a published procedure [3].

In the second step, by texture analyzer adhesion was evaluated. We used Stable Micro Texturometer (United Kingdom) with modified cylinder probes.

RESULTS: Texture profile analysis as an analytical method can easily quantify multiple textural parameters, for matrix systems this measurement provides e.g. adhesion. Summarizing the re-

sults of all measurements we found differences related to the type of polymer and the concentration of polymer in all tested parameters.

CONCLUSIONS: The most promising formulations were matrix systems containing chitosan and gelatin, which will be evaluated in further experiments.

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P1/11

Pharmaceutical development and in vitro evaluation of novel core-shell microcapsules for topical delivery of berberine

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INTRODUCTION: The objective of the study was to develop a novel all-natural carrier, based on core-shell microcapsules, for topical delivery of berberine. This system is designed for the improvement of skin conditions such as acne, as an alternative to the conventional topical therapy.

MATERIALS AND METHODS: Berberine is an isoquinoline-alkaloid derivative frequently reported for antimicrobial activity against Gram-positive and Gram-negative bacteria, antiinflammatory and antiandrogenic effects. The broad spectrum of pharmacological activities makes berberine a potential candidate in acne therapy. However, poor bioavailability, due to low water solubility has limited the clinical applications of berberine. This drawback could be overcome by the microencapsulation technology that uses microcarriers in protecting, transport and delivery of hydrophobic compounds.

Firstly, microparticles $CaCO_3$/BSA were obtained by coprecipitation of $CaCO_3$ with BSA, followed by layer-by-layer deposition of the pectine hydrogel formed by cross-linking of pectin with Ca^{2+} from microparticles and subsequently formation of polyelectrolyte complex pectine/chitosan. After removing of $CaCO_3$ from the microparticles by complexation with EDTA, microcapsules with BSA gel in the core were obtained by thermal treatment. Determination of Encapsulation Efficiency (%) and Loading Efficiency (%) for berberine was assessed by UV-Vis spectrometry; the characterization of microcapsules with/without encapsulated berberine, have been made by FTIR, XRD, CLSM and SEM. In vitro release study in different pH conditions was performed in order to study the release profile of berberine from microcapsules.

RESULTS: The mean size of microcapsules was 5-7 μm and the UV-Vis quantitative study of encapsulating and loading efficiency showed a low encapsulation, specific for hydrophobic active agents. Although, the drug release profile revealed a sustained release of berberine, with best results for pH 4.0 sodium acetate buffer.

CONCLUSION: Based on the obtained results, we can conclude that, the core-shell microcapsules made of BSA gel core and a polyelectrolyte complex pectin/chitosan multilayer shell represent a promising carrier for targeted and prolonged delivery of berberine.

P1/12

Proposal of a pharmaceutical form for cosmetic use with volatile oil of Anethum graveolens and evaluation of its effectiveness

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INTRODUCTION: The volatile oil of Anethum graveolens (Umbeliferae) is well known and used for the pharmacodynamic hepatoprotective, antimicrobial, hypoglycemic and even galactogog effect [1,2,3].

In addition, it is traditionally classically known for its phytoestrogenic effect. The purpose of the present paper was to: 1) evaluate the chemical composition of the volatile oil of Anethum graveo-

lens by GC-MS 2) formulate a pharmaceutical form for skincare with antiaging properties 3) to check the effectiveness on the volunteers.

MATERIAL AND METHODS: The study utilized GC-MS from the Banat`s University of Agricultural Sciences, a cutaneous biometric apparatus with components: corneometry, elastometry, sebometry, produced by Courage-Khazaka. Volunteers accepted into the study were selected based on admission criteria.

RESULTS: The chemistry study revealed the following composition: 13 major components were identified in the Anethum graveolens essential oil : Trans-beta-ocimene: 0.138, Lavandulol: 0.065, Alpha-phellandrene: 1.499, pcymene: 0.211, D-limonene: 73.546, 2-Ethylacrylonitrile: 0.049, 1-Butene: 0.007, Norbornane: 1.067, Estragole: 0.121, Piridine: 0.064, D-carvone: 17.829, 1H-Imidazole: 0.014, Anethole: 4.981.The biometric assessment study revealed: 1) regardless of age there is a gradual increase in elasticity (2) hydration and seborrhea increase transient only upon application while elasticity remains significantly increased at the end of 60 days of testing 3) the proposed cosmetic product with Anethum graveolens oil is compliant and does not produce adverse effects.

CONCLUSIONS: The Anethum graveolens oil deserves to be reconsidered as a cosmetic active substance and not only aromotherapic agent.

Aknowledgements: Special thanks to the Favisan laboratories

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P1/13

Microemulsion-based hydrogels with clotrimazole – design of formulation and evaluation of antifungal properties

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INTRODUCTION: Microemulsions are colloidal dispersions with nanometric droplets size in the range of 5-200 nm and they are produced by spontaneous mixing oil and water phases [1]. Unique solubilization properties of microemulsions make them potential carriers for topical application of poorly water soluble drugs (e.g. clotrimazole) [2]. Limitation of using microemulsions as dosage form for topical delivery is their low viscosity. Incorporation of microemulsion into hydrogel structure improves application features and enables to use them in dermal formulations [1, 3]. In this study, microemulsion-based hydrogels with clotrimazole were designed and their antifungal activity comparing to hydrogel with traditional emulsion was performed.

MATERIALS AND METHODS: Pseudo-ternary phase diagrams for microemulsion regions were constructed using different oils and surfactants [4]. To prepare hydrogels Carbopol® 980 was used as a gelling agent. Antifungal activity was evaluated against yeast cultures Candida parapsilosis ATCC 22019, Candida krusei ATCC 6528 and clinical strains belonging to C. albicans and C. parapsilosis species using zone inhibition method.

RESULTS: Based on the data obtained from pseudo-ternary phase diagrams, two optimal compositions of micromulsion were selected (oleic acid/Tween 80 and Capryol® 90/Tween 80). It was shown that in all tested yeast cultures zone inhibition of designed microemulsion-based hydrogels was higher than hydrogels with traditional emulsion.

CONSLUSION: Using microemulsion as carrier of clotrimazole improved antifungal activity of prepared hydrogels.

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P1/14

Formulation and pharmaceutical evaluation of topical foams

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INTRODUCTION: 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.

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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P1/15

Application of image analysis in the development and optimization of pharmaceutical foams

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INTRODUCTION: Foams, that are colloid systems where the gas phase is dispersed in the continuous liquid phase, are used in several areas including pharmaceutics and cosmetics. Foams containing active ingredients for pharmaceutical purposes are mainly applied dermally, but vaginal and rectal, as well as solid foams are available. The increasing number of topical foam formulations relates to the numerous advantages they have compared to conventional creams or ointments – easier and more comfortable application even on large skin, sensitive or hairy areas resulting in better patient compliance. Good spreadability without oily residues on the skin and good rate of drug transfer can be provided given proper composition and formulation.

Other than surface active agents, foams can contain active pharmaceutical ingredients, solvents, co solvents and depending on the container – propellant. Medicated foams are characterized by pharmacopoeial tests to determine relative density and duration of expansion for pressurized formulations.

MATERIALS AND METHODS: The examined foams were generated from emulsions composed of distilled water and various oil phase (eg. sunflower oil) by using distinct surface active agents (eg. Tween 80, Span 80). Image analysis (Nikon SMZ1000, Image J) of foams provides information on the structure, the individual cell size and shape, therefore can also be used to examine and evaluate the break down progress of the different foam compositions.

RESULTS: The impact of type and ratio of excipients was followed by the morphological parameters (shape, size distribution, width and variability, etc.) of the foam image analysis.

CONLUSIONS: Foam characteristics are influenced and can be optimized by the composition, the type and amount of detergent. Altering the amount and type of surface active ingredients effect the shape, size distribution of foam cells resulting in modified relative foam density.

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P2- NANOPARTICLES 1.

P2/1

Optimization and Charecterization of Nanosuspension of Cilostazol by Smart Particle Size Reduction (Top Down) Approach

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INTRODUCTION: The water solubility, dissolution rate and gastrointestinal permeability are fundamental parameters that control rate and extent of drug absorption and its bioavailability. Particle size reduction is one of the oldest strategies for improving solubility of poorly soluble compounds that can be applied to nano-specific formulation for many years. The nanonization of the API leads to an increase in their surface area which proportionally increase the dissolution rate and the saturation solubility, subsequently improve the bioavailability of poorly water soluble drugs and may also decrease systemic side effects. Cilostazol (CLZ) is one such molecule which belongs to Biopharmaceutical Classification System (BCS) Class II based on poor solubility and high permeability. In USA CLZ is approved for a treatment of Intermittent Claudication and in Japan is approved for a treatment of Ischemic Symptom.

MATERIALS AND METHODS: The main goals of this study were to compare the most commonly utilized top down approaches by optimization of the milling and the high-pressure (HPH) parameters to achieve CLZ nanocrystals and to improve the long term stability of the formulation applying freeze drying technique. The particle size reduction techniques were used to improve dissolution rate and water solubility of Cilostazol (CLZ). The nanosuspension was characterized using DLS method, zeta potential measurment, spectroscopic methods (DSC, FTIR, XPRD), in-vitro thermodynamic solubility and in-vitro dissolution studies.

RESULTS: Nanosuspensions made by both techniques significantly increased the dissolution rate and saturation solubility compared to the pure drug powder and the unmilled product. Spectroscopic studies confirmed partial crystalline to amorphous transitions.

CONCLUSIONS: Both techniques are suitable to create nanosuspensions of CLZ, but by wet ball milling process lower intensity weighted mean hydrodynamic diameter and polydispersity index values can be achieved. These methods are suitable for improving the dissolution rate and water solubility by setting the right parameters and carefully choosing the right components.

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P2/2

Scaling up of combined wet milling process

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INTRODUCTION: Wet milling technologies are industrially used processes. These methods are applicable for micronization but is usually used for nanonization [1].

The process we used is a combined wet milling technology of wet stirred media milling and planetary ball milling. The nanonization of the particles was successfully achieved by optimization of process parameters (particle size distribution of 100-500 nm) [2].

In this work our aim was to discover the robustness of the combined wet milling process in order to improve the process productivity.

MATERIALS AND METHODS: Meloxicam (MEL) [4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)- 2H-benzothiazine-3-carboxamide-1,1-dioxide] (EGIS Ltd., Budapest, Hungary)

Poly(vinyl alcohol) (PVA)-Mowiol 98-4 Mw~27000 (Sigma Aldrich Co. St. Louis, U.S.)

Wet milling process: In the milling jar from 0.50 g to 5.00 g of MEL was suspended in 15.00 g-19.50 g of 5% PVA solution. The milling process was performed using Retsch PM100 planetary ball mill (Retsch GmbH, Haan, Germany).

Particle size measurement: Malvern Mastersizer Hydro 2000S unit (Malvern Instruments Ltd., Worcestershire, UK).

Differential scanning calorimetry (DSC): Mettler Toledo DSC 821e thermal analysis system (Mettler Inc., Schwerzenbach, Switzerland).

Thermogravimetric analysis: Mettler–Toledo TGA/DSC1 (Mettler–Toledo GmbH, Switzerland) instrument.

X-ray powder diffraction analysis (XRPD): Bruker D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany).

RESULTS: The right quality products of the trial range were the samples with the MEL content from 2g to 4g. Amorphous content of the drug is inversely proportional to the amount of drug. The higher amount of active agent results in decrease of degree of amorphization.

CONCLUSION: In case of combined wet milling process, the active agent amount may be important parameter of design space because the material to be milled can also increase the efficiency of milling and its robustness (within a given particle size range) and it may affect the retention of crystallinity

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P2/3

Preparation and characterization of fenofibrate-loaded electrospun microfibers

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INTRODUCTION: Drugs displaying poor water-solubility often require high doses in order to reach therapeutic efficacy. In case of drugs displaying good permeability, but low solubility, improvement in the extent and rate of dissolution can improve oral bioavailability. Out of the numerous methods available for solubility enhancement, electrospinning has emerged as a relatively simple and effective method for obtain improved dissolution of embeded actives.

Fenofibrate, the frequently prescribed antilipidemic agent from BCS class II, displays high lipophilicity and low water solubility, which in terms limits its oral absorbtion.

MATERIALS AND METHODS: Viscous polymeric solution for electrospinning were prepared by solubilizing Fenofibrate (micronized, obtained from a local pharmaceutical company) in Tween 80 and mixing with 20 % (m/w) ethanolic PVP K29/32 solution (ISP Pharmaceuticals). Microfibers were prepared by feeding the prepared gels with a rate of 1.0 mL/h, through a 1.2 mm internal diameter needle. High-voltage (aprox. 20 kV) was applied at 10 cm collector-needle distance. The obtained fibers were dried at room temperature and were analyzed in terms of fiber diameter, morphology, thermal analysis, disintegration and dissolution characteristics.

RESULTS: Uniform beadles fibers were obtained during the electrospinning process, with mean diameter of 1.52 ±0.29 μm. Given the high surface-to-volume ratio and high porosity of the fibers, the prepared mats disintegrated instantaneously. Thermoanalytical characterization of the obtained microfibers implied the crystalline-amorphous transition of the active, which, along with the increased specific area enabled rapid and complete dissolution of the poorly soluble drug.

CONCLUSION: Fenofibrate-loaded electrospun PVP-based nanofibers proved to be an excellent choice for improving the solubility of the BCS II class drug, which could be a promising alternative for improving the oral bioavailability of the drug and subsequently reduce its dose.

P2/4

Investigation of continuous downstream processing of drug-loaded electrospun polymer nanofibres

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INTRODUCTION: Preparation of polymer-based electrospun amorphous solid dispersions is a promising way to enhance the dissolution of poorly water-soluble drugs which lead to improved bioavailability in many cases [1]. However, there are some difficulties in practical application of electrospinning such as scaling-up of the technology, stability of the electrospun product and achieving of the whole downstream process to generate tablet form [2]. During this research, the above mentioned challenges were investigated

and the current trends of the pharmaceutical field, continues technologies were keep in mind.

MATERIALS AND METHODS: Compositions of PVPVA64 and 40% model drugs (spironolactone, itraconazole) were dissolved in EtOH:DCM 1:2 mixture for electrospinning experiments. Morphology and amorphous form of the products were examined by scanning electron microscopy, differential scanning calorimetry and X-ray powder diffraction while the dissolution measurements were accomplished on a Pharmatest PTWS 600 dissolution tester (Pharma Test Apparatebau AG, Germany). A well-seeming technology which called high speed electrospinning (Quick2000 Ltd, Hungary) was applied for getting higher productivity. Furthermore, different steps of a possible electrospinning-based continuous downstream process were tested by using loss-in-weight feeder, a Dott Bonapace CPR6 eccentric tableting machine (Limbiate, Italy) and a Kaiser RamanRxn2® Hybrid in situ analyzer (Kaiser Optical Systems, USA).

RESULTS: Based on the results, it can be stated that the high speed electrospinning increased the productivity more than thirtyfold compared to the single needle method. In addition, downstream process of the electrospun products also seemed to be feasible and the experiments bear out the applicability of this technology in a continuous process line. Nevertheless, Raman-spectroscopy measurements prove that crystalline traces have remarkable impact to the dissolution of amorphous solid dispersions.

CONCLUSION: High speed electrospinning opens a new way to the pharmaceutical application of drug-loaded electrospun materials. Improved productivity makes possible to investigate continuous downstream process steps of the products where application of in-line analytical devices is necessary due to the significant correlation between crystalline content and dissolution.

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P2/5

Characterization of electrospun loratadine-PVP composite nanofibers prepared by a 3D-printed electrospinning apparatus

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INTRODUCTION: Nanofibers are a convenient solution to the current problems of drug delivery due to their high surface-to-volume ratio architecture [1]. Electrospinning is the most preferred technique for nanofiber fabrication due to its simplicity, cost-effectiveness and flexibility [2, 3]. The objective of this project was to develop pharmaceutical nanofibers with a 3D printed poly lactic acid (PLA) chamber using loratadine (LOR) as model drug and PVP (MW 1,300,000) as the filament-forming matrix.

MATERIALS AND METHODS: Solutions of PVP in ethanol were used to fabricate LOR. A ratio of 1:1 LOR to PVP was used during the procedure. The solutions were electrospun in a 3D-printed electrospinning chamber, made of PLA. A syringe pump provided the solution to the nozzle inside the electrospinning chamber, with speed of 15 μl/min. The potential difference was 35 kV between the nozzle and the rotating grounded collector. Two different working distances were set between the nozzle and the fiber collector (6.5 and 9.5 cm). Further, reference samples were prepared by solvent evaporation (SE) of 1:1 LOR to PVP from ethanol solution. Diameters of the nanofibers were measured by Scanning Electron Microscopy (SEM) image analysis. Moreover, Fourier Transform Infrared (FT-IR) Spectroscopy was used to identify the interaction between PVP and LOR. Differential Scanning Calorimetry (DSC) and X-Ray Diffraction (XRD) analysis was carried out to assess the crystallinity and the changes in the crystalline pattern. The in vitro release was also tested.

RESULTS: LOR loaded 4 wt% PVP solutions produced homogenous and intact nanofibers. Major bands of LOR in FT-IR were clearly observed in the spectrum the nanofibers. Moreover, DSC thermograms indicated that LOR existed in its amorphous dispersed state within PVP fibers. This is also supported by the disappearance of the melting peak at 135 °C and the complete absence of LOR crystals under SEM. Lastly, the XRD patterns also confirmed the amorphous nature of the prepared nanofibers. The in vitro release showed an enhancement of LOR release.

CONCLUSION: Amorphous loratadine-PVP nanofibers were produced using an inexpensive 3D-printed electrospinning apparatus for drug

formulation. The produced nanofibers had increased drug release, meaning increase of bioavailability.

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P2/6

Optimization of spray-dried zidovudine-loaded chitosan microparticles using experimental design approach

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INTRDUCTION: Spray drying is an advanced, easy to scale-up technique of micro- or nanoscale multiunit carriers preparation [1, 2]. This method is uncomplicated, but in order to obtain product with desirable properties, careful adjustment of the spray drying parameters is required. Thus, the aim of the current study was to examine the interference of different variables in order to optimize spray drying of zidovudine-loaded microparticles (MPs) intended for local delivery, with the use of Fractional Factorial Design (FFD). Low-molecular weight chitosan and chitosan glutamate - water-soluble chitosan derivative, were employed for MPs preparation.

MATERIALS AND METHODS: In order to select variables significantly influencing MPs preparation, namely the type and concentration of the polymer, drug to chitosan ratio, the presence of additional co-solvent, inlet temperature and feed rate, two-level FFD with 3 center points was implemented.

RESULTS: Overall, as a result of 11 experiments, MPs formulations with chitosan or chitosan glutamate were prepared and characterized in terms of shape, size, moisture content, encapsulation efficacy and production yield. Attained results indicate that inlet temperature had an impact on the entrapment efficiency whereas drug loading was influenced by both drug to polymer ratio and inlet temperature. In turn, feed rate and type of chitosan used were found to be significant in respect of moisture content. Additionally, obtained model suggests that chitosan glutamate should be the polymer of choice for MPs preparation.

CONCLUSION: These results are useful in limiting the range of selected variables, enabling to plan experimental domain for spray-drying experiments more precisely in order to produce chitosan MPs with feasible characteristics for delivery of zidovudine.

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P2/7

Physicochemical characterisation and cyclodextrin complexation of baicalin

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INTRODUCTION: Baicalin is a flavone glycoside, extracted from the root of Scutellaria baicalensis. It was shown, that the poorly water soluble and poorly permeable (BCS IV) compound has remarkable pharmacological effects including antioxidant, antimicrobial and antitumor actions [1]. The low oral bioavailability (2.2% in animal modells) of this drug could be alleviated through cyclodextrin (CD) inclusion complexation. CDs are cyclic oligosaccharides composed of 1,4-linked D-glucopyranose units possessing a hydrophilic exterior and hydrophobic cavity [2]. The physicochemical profiling of baicalin (lipophilicity, acid-base properties, solubility) is essential in order to develop CD-based carrier systems. The scope of the work was the biorelevant physicochemical profiling of baicalin in terms of acid-base properties, lipophilicity, thermodynamic solubility and CD complexation analyzed by phase solubility, UV and NMR experiments.

MATERIALS AND METHODS: The solubility of baicalin was characterized by phase solubility studies, the stability constant of the complexes were determined according to Higuchi-Connors. To ascertain the structure of the inclusion complexes between baicalin and CDs, 1H NMR spectroscopy studies of free drug and host-guest complexes were undertaken. Partition coefficient measurements were carried out by the stir-flask method, the determination of protonation constants was fullfilled by 1H NMR–pH titration. Solid complexes of baicalin and CDs were formulated by freeze-drying and extrusion.

RESULTS: RAMEB, SB-ß and gamma-CD significantly enhanced the poor aqueous solubility of baicalin and displayed AL and BS-type phase diagrams. 1H NMR confirmed the formation of inclusion complexes. Thermodynamic solubility was measured in various biorelevant media and compared to compendial media.

Preformulation studies are necesarry to formulate drug delivery systems. CD encapsulation of drugs is well-known in the scientific literature; our results showed that baicalin can also form inclusion complexes.

CONCLUSION: The study proved that CDs are ideal carriers for baicalin. Biorelevant physicochemical profiling of baicalin was carried out and the results can be used to determine the best formulation path.

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P2/8

Formulation and investigation of meloxicam-albumin nanoparticles prepared by coacervation method

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INTRODUCTION: Bovine Serum Albumin (BSA) is playing an increasing role as a nano Drug Delivery System (nanoDDS) in the clinical therapy. Due to its biocompatibility and non-toxicity, it can be used as a pharmaceutical carrier for different drugs more safely versus many synthetic polymers. BSA is also an excellent material to construct nanoparticles (NPs) 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 NPs. Our aim was to formulate BSA based NPs, which have appropriate drug release.

MATERIALS AND METHODS: Meloxicam (MEL) (Egis Pharmaceuticals Plc. Hungary) a BCS class-2 substance as model drug was chosen to the experimental work and BSA fraction-V (Alfa Aesar, UK) was selected as nanoDDS. BSA based MEL NPs were prepared by means of coacervation method [1]. The optimization of formula was carried out using factorial design. According to the design the optimal formula was prepared and further investigated. BSA was dissolved in phosphate buffer (pH=7.4) and MEL dissolved in ethanol was added to the BSA solution under constant stirring. For cross-linking glutareldehide was used [2]. After purification freeze-drying was carried out. The particle size and zeta potential were determined. Fourier-transform infrared spectroscopy (FTIR), thermal analysis (TA) and X-ray powder diffraction (XRPD) were used as physicochemical characterization methods. Dissolution studies were carried out using UV spectroscopy to investigate the drug release.

RESULTS: The desired particle size (130 nm) and zeta potential (-31.8 mV) was reached by optimization of the formula. Based on the FTIR data trehalose partially prevented structural perturbations in BSA upon freeze-drying. TA and XRPD analysis showed the NPs are thermal stabile and semi-crystalline. Dissolution studies showed increased drug release in comparison to the physical mixture.

CONCLUSION: Using factorial design BSA based MEL containing NPs were prepared by means of coacervation and freeze-drying with desired properties (size, zeta potential, stability). The optimized formulation can be applied for drug conjugation to help the therapeutic effect.

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P2/9

Optimization of gelatin/alginate complexe coacervation to encapsulate a hydropholic drug

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INTRODUCTION: The biopolymers are synthesized in the plants or the animals by enzymatic way and are of this fact quickly degraded in a biological environment. Many biopolymers was studied and used in the microencapsulation of pharmaceutical product, in this study we undertook the encapsulation of paracetamol by using two biopolymers (Gelatin and Alginate).

The aim of the current work was to develop a microparticulate system based on complexe coacervation between gelatin and alginate to encapsulate paracetamol. Various formulations were prepared using the respose surface methodology to study the effect of some factors on the chosen response.

MATERIALS AND METHODS: The objective of this work is to study the influence and the interaction of different factors (surfactant concentration, first homogeneisation speed and the second homogeneisation speed on the process of microencapsulation using an experimental design for the preparation of paracetamol microparticles by complex coacervation using gelatin and alginate as biopolymers.

RESULTS: The morphology of all the microcapsules made was analyzed with a microscop. They appeared transparent, spherical and distinct from each other. The values of microencapsulation yield calculated for each configuration; the different tests show that paracetamol encapsulation yield varies between 31% and 75 %.

The effects of each variable make possible the evaluation of their action when the parameter passes from its low level to its high level. The other parameter being fixed at the center of his experimental reference mark (centered value).

CONCLUSIONS: Using all the results obtained in the studies carried out on the influence of the chosen parameters on the selected answer and with the help of the used software used, we can distinguish a zone of the experimental domain which make possible the optimization the microencapsulation process by complex coacervation.

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P2/10

Formulation and investigation of amphiphilic graft co-polymer based polymer micelles

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INTRODUCTION: Polymeric micelles present a promising tool to increase bioavailability and change the toxicological profile of the encapsulated drug. Their particle size is around 80 nm, which is optimal for passing the physiological barriers. Soluplus® (BASF GmbH, Germany) is a novel solubilizing amphiphilic graft co-polymer (Mr = 90 000-140 000 g/l), which is polymerized from polyethylene glycol 6000 (PEG 6000), vinyl caprolactam and vinyl acetate in a ratio of 13:57:30, offers the possibility of a good solubility enhancement in combination with a fast dissolution to drug loaded polymer micelles. Its CMC is 7.6 mg/L and HLB value is approx. 13. Our current project's aim is to formulate polymeric micelles with a model drug due to the extensive therapeutic use and numerous indications.

MATERIALS AND METHODS: Methanol, ethanol, 2-propanol, acetone and acetonitrile (Merck Ltd., Budapest, Hungary) as solvents were used for preparation of polymeric micelles [1]. The model drug was dissolved in the organic solvents under constant stirring and 1% NaOH was used for setting the pH [2]. Each solution was investigated at alkaline and neutral pH using 10% hydrochlorid acid adjusting the pH on 7.0. To form the micelle Soluplus® was added to the solution. The organic solvent was evaporated with vacuum distillery and the polymeric micelles precipitated. The particle size and zeta potential was measured using Malvern nanoZS instrument (Malvern, Wercestershire, UK). To investigate, whether the formed polymer micelles contain a drug, absorption spectroscopy methods were used.

RESULTS: The precipitate was easily dissolved unlike the original material which was a good sign that we improved the solubility. The particle size

is acceptable by the EMA regulations, 50% of the particles are under 100 nm size, they are around the ideal 80 nm even before membrane filtering it. The zeta potentials are the appropriate value, they promise complying stability. Spectroscopic studies showed fast drug release of the formulation.

CONCLUSION: We can conclude Soluplus® is a good excipient for the preparation of polymer micelles. Formulating polimer micelles can improve the solubility of poorly soluble agents, which can be useful for developing "value added" preparations.

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P2/11

Design and Development of microcarriers for natural drug encapsulation: Statistical validation and optimization of polydispersity index and volume/surface parameters

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INTRODUCTION: Recently, the formulation of natural drugs such as plant extracts and essential oils (EO) has been highly studied due to their multitude bioactivities and their lot off applications from food flavor industry to pharmaceutical and cosmeceutical applications [1].

In aims of Design and Development of EO microcarriers, Ionic Gelation (IG), highly recommended for the encapsulation of hydrophobic bioactive molecules, can be applied and optimized to ensure high drug encapsulation yield with response stability to facilitate its semi-industrial scaling-up [2].

MATERIALS AND METHODS: To obtain EO microcarriers with small particles size and high drug loading capacity, the studied EO was microencapsulated by cross-linking a biodegradable polymer under several experimental conditions. Process optimization was carried out using the Response Surface Methodology to investigate fourth experimental parameters (polymer concentration, cross-linking agent concentration, mixing time and mixing velocity) and the statistical analysis was performed using one-way analysis of variance (ANOVA) and the Mean comparison of Polydispersity Index (PI), volume-weighted mean particle diameter (d43) and Surface Weighted Mean particle diameter (d32) was carried out using T-test [3]. All analyses were repeated in triplicate.

RESULTS: Both the loading capacity and the particles size of the obtained microcapsules were evaluated to optimize the ionic gelation process. Laser diffractometry (Mastersizer 2000, Malvern Instruments Ltd) was used to assess the physical characteristics of the developed microcarriers.

The selected optimal conditions allow obtaining microparticles with a loading capacity of 4.95 to 15.19% with a PI range from 0.852 to 5.695, a specific surface area from 0.011 to 10.1 m2/g, a d32 range of 0.595 to 547.735 μm and a d43 from 5.392 to 714.263 μm. The RSM results combined with the statistical analysis allow assessing the correlation between the fourth experimental parameters and their range on significant (P-value < 0.05) or not significant (P-value > 0.05) effects.

CONCLUSION: Development of microcarriers for EO encapsulation using alginate microspheres was optimized to allow an interesting loading capacity, acceptable particles size, desired polydispersity and suitable volume/surface characteristics. The designed microencapsulation process is statistically validated and can be easily scaling-up to a semi-industrial level.

P2/12

Nanostructured lipid carriers for Alzheimer's disease treatment: Influence of solid/liquid lipid ratio on physico-chemical properties

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INTRODUCTION: Novel formulations based on embedded herbal therapeutical moieties into nanostructured lipid carriers (NLC) for nose to brain delivery are promising candidates for multitarget therapy of Alzheimer's disease along with specific and selective delivery to the brain tissue. Given that NLC effectiveness would be determined by their physico-chemical properties, the aim of this study was to investigate the influence of solid/liquid lipid ratio upon them.

MATERIALS AND METHODS: NLC loaded with dry extract of Salvia officinalis L. (SE) were prepared by solvent evaporation method [1]. Lipid phase consisted of phospolipon 90H (kindly donated by Phospholipid, Germany) and oleic acid (Sigma-Aldrich, Germany) in ratio of 1 to 0.216 (NLCS1), 0.433 (NLCS2) and 0.866 (NLCS3). Relative ratio of phospolipon 90H to other NLCs` formulation variables was 1 to 28.67, 0.167, 1.67, 0.3 and 58.7 for ethanol (Alkaloid, Macedonia), SE, tween 80 (Merck, Germany), poloxamer 407 (BASF, Germany) and water, respectively. NLCs` morphology (Jeol-SEM T300, Japan), particle size (PS) and size distribution (PSD) (Mastersizer 2000, UK), zeta potential (ZP) (Nano ZS, UK) and encapsulation efficiency (EE%) (HPLC Agilent 1100, Germany) were determined.

RESULTS: SEM photomicrographs pointed that prepared NLCS were with spherical shape and smooth surface. As they were yellow-green in color DLS technique could not be used for PS and PSD, so laser diffractometry was applied. By increasing the amount of liquid lipid, NLCs` PS increased (132±1.8, 145±0.86 and 257±6.33 nm for NLCS1, NLCS2 and NLCS3, accordingly) most likely related to the higher density of organic solution thus resulting with larger emulsion droplets with lower surfactant surface coverage. Span values indicated narrow PSD for NLCS1 (1.05±0.01) and NLCS2 (1.04±0.06), while NLCS3 PSD (1.93±0.04) was a bit wider. Amount of liquid lipid did not have influence on ZP (-17.3±0.41 mV), contrary to the EE% (NLCS1 - 42.03±1.23, NLCS2 – 48.94±1.85 and NLCS3 – 95.34±2.21%) probably due to the increase of imperfection degree in the solid lipid crystals, thus providing more space for SE encapsulation.

CONCLUSION: Influence of solid/liquid lipid ratio on NLCS physico-chemical properties was determined. Results indicated statistically significant influence on PS and PSD, as well as EE%.

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P2/13

Determination of Load-Efficieny of Vancomycin in Nanoparticles System

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INTRODUCTION: Vancomycin is a glycopeptide antibiotic which is active against gram-positive organisms. It is used particularly in the treatment and prophylaxis of staphylococcal infections especially caused by Methicillin-resistant Staphylococcus aureus. To eliminate adverse effects such as ototoxicity and nephrotoxicity of vancomycin upon systemic administration, local administration with various drug delivery systems such as microspheres or nanoparticles can be utilized. Chitosan is a polysaccharide produced by N-deacetylation of chitin. Chitosan is biocompatible, biodegradable and non-toxic material. Fucoidan is another polysaccharide obtained from brown seaweeds. It has anticoagulant, antithrombotic, antivirus, antitumor and immunomodulatory, anti-inflammatory and antioxidant properties. Chitosan and fucoidan due to their positive and negative charges in proper media respectively, forms a nanoparticle system in which active pharmaceutical ingredients can be encapsulated. In this study, vancomycin-loaded chitosan/fucoidan nanoparticles were fabricated and for determination of load efficiency of vancomycin, an easy and effective method was developed.

MATERIALS AND METHODS: Nanoparticles were prepared using polyion complexation method. For this purpose chitosan was dissolved in 1% (w/v) acetic acid solution while fucoidan and vancomycin were dissolved in distilled water. Fucoidan solution was then dropped to chitosan solution under magnetic stirring. Nanoparticles were seperated by centrifugation and then freeze dried.

RESULTS: Two methods were tested, UV spectrophotometry where samples scanned at 280 nm wavelength and RP-HPLC method for related substances in European Pharmacopeia monograph for vancomycin with modification.

Determination of vancomycin amount by using UV spectrophotometry couldn't be achieved due to interference of fucoidan remains in supernatant since fucoidan give absorbance at same wavelength for vancomycin. By using RP-HPLC, one principal peak was obtained with the injection of sample in the chromatographic system and it was identified as vancomycin with standart solution.

CONCLUSION: RP-HPLC method can be used for determination of vancomycin which remains in solution.

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P3- OCULAR/NASAL/PULMONAR DELIVERY

P3/1

QbD approach to development of solid lipid microparticles as dry powders for inhalation

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INTRODUCTION: Solid lipid microparticles (SLMs) combine several features that are important for successful delivery of drugs to the lungs in the form of dry powders for inhalation (DPIs). Due to the presence of lipid excipients, SLMs can be tailored to have the appropriate flowability and their low density further provides decrease in the aerodynamic diameter of DPI particles [1]. The aim of this study was to evaluate, according to the Quality by Design (QbD) principles, the influence of the processing and formulation parameters on the properties of the prepared SLMs.

MATERIALS AND METHODS: SLMs were prepared by the melt emulsification method. Emulsions consisting of salbutamol-sulfate (SS), water and 5% of the lipid phase were prepared, according to the two level resolution V design by varying the four parameters: lipid type (glyceryl dibehenate or stearyl alcohol), surfactant Poloxamer 188 concentration (0.4 or 1.5%), high-shear mixing time (2 or 8 minutes) and drying method (freeze or spray drying). Particle size was determined by the laser diffraction technique (Mastersizer, Malvern, UK) and flowability was evaluated by calculating Carr's index (CI) and Hausner ratio. The SS content was assayed by liquid chromatography tandem - mass spectrometry (TSQ Quantum Access MAX).

RESULTS: The results revealed that by prolonging the high-shear mixing time particles of smaller size were obtained (11-15 μm); whereas the span was higher in the case of glyceryl dibehenate formulations (2.6 vs 2.0 for stearyl alcohol). CI was less than 25% in almost all formulations, indicating good flow properties [2]. The SS loading in SLMs that were freeze dried was 0.5-2.5%, in comparison to the 8.9-11.5% for the spray dried particles, which was expected due to the SS hydrophilic properties.

CONCLUSION: Based on the obtained results, it can be concluded that both formulation and processing parameters need to be considered for development of SLMs with the properties appropriate for DPIs.

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P3/2

Characterization of biodegradable nanoparticles for pulmonary delivery of a flavonoid

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INTRODUCTION: Pulmonary drug delivery is a non-invasive approach in the treatment of respiratory or systemic diseases. It allows direct targeting of the natural therapeutic agents such us api-

genin. This flavonoid has remarkable antioxidant activity, moreover, is able to inhibit cell proliferation, migration and induce apoptosis in lung cancer cells (H1299, H460 and A549) [1]. The effectiveness of an inhaled bioactive component depends of the particle size, morphology and aerosol characteristics, as well as pulmonary physiology. Biodegradable nanoparticles offer improved drug solubility, increased local drug concentration and targeted site of action [2].

MATERIALS AND METHODS: To prepare biodegradable nanoparticles, locust bean gum and chitosan biopolymers were used. High pressure homogenization was applied to encapsulate apigenin. The physical properties of the particles such as size, charge and drug loading efficiency were measured. The dissolution of Api was determined with Franz cell apparatus in simulated lung fluid. The samples were further lyophilized with carrier and residual water content was measured by Karl-Fischer titration. The morphology of dry powders was observed with scanning electron microscopy. In vitro aerodinamical properties of the carrier-based dry powders were investigated by next generation cascade impactor (NGI).

RESULTS: The developed biocompatible nanoparticles had adequate size and apigenin could be effectively loaded with high pressure homogenization. The optimized freeze-drying conditions were suitable to produce particles with low residual moisture content and the particle size was maintained following a rapid rehydration. The dissolution was enhanced compare to the raw apigenin. The in vitro aerosol characterization indicated that the excipients play an important role in the deposition of biopolymer based nanoparticles.

CONCLUSION: The developed biodegradable particles may have great potential for pulmonary drug delivery of bioactive agents.

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P3/3

Development of novel formulated meloxicam potassium containing dry powder inhaler systems

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INTRODUCTION: Cystic fibrosis (CF) is an autosomal recessive hereditary disease that can't be cured by the current state of science. There are a chronic bacterial infection and inflammatory epithelial cell layer in the lung. NSAIDs (e.g. meloxicam potassium, MXP) have relevance in CF [1]. Dry powder inhalers (DPIs) are an evolving sector due to their many advantages. Based on formulation there are two groups of DPIs. For the exploitation of their beneficial features, the aim of our work was the development of novel combined DPI formulations, thus the use of a spray dried drug on a (surface modified) carrier. We expected a favorable change in interparticle interaction and thus improved aerosolization and high lung deposition (determined by Fine Particle Fraction (FPF)).

MATERIALS AND METHODS: MXP (Egis Plc., Hungary) was applied as a model drug. Spray drying was used to enhance the aerosolization properties of this agent (MXPspd). Inhalac® 70 (IH 70) was used (MEGGLE Group, Germany) as a carrier. Magnesium stearate (MgSt) (Sigma-Aldrich, Hungary) was applied as a surface modifier of the carrier. The surface treatment of the carrier and the adhesive mixtures were prepared by physical mixing with Turbula mixer (W. A. Bachofen AG, Switzerland). Samples were prepared to contain MXP, MXPspd; and their powder mixtures with IH70 and IH70-MgSt. We investigated the particle size distribution, the morphology, the structure of the samples. The adhesion and cohesion works were analyzed. The aerosolization efficacy was determined with the Andersen Cascade Impactor.

RESULTS: The investigations revealed that the spray drying procedure resulted in amorphous, spherical MXP particles with 2 μm as mean size. The FPF (~60%) of these particles exceeds the traditional, carrier-based products (FPF 20-30%), which can be traced back to structure and mor-

phology of the sample. Among these particles, there is a high cohesion work. Furthermore, application of these particles of a surface modified carrier – the novelty of this work – (which affects the interparticle interactions) further improved the FPF (~72%) result.

CONCLUSION: The presented novel formulation technology is a new milestone to further increase the lung deposition of MXP, which can increase the effectiveness of CF therapy.

ACKNOWLEDGMENT: This project was supported by EFOP-3.6.2-16-2017-00006 project and Gedeon Richter Plc. Centennial Foundation.

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P3/4

Development of antibiotic dry powder inhalation system based on Quality by Design methodology

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INTRODUCTION: Antibiotic delivery as dry powder inhaler (DPI) has been efficaciously studied for achievable clinical treatment of respiratory tract infections. DPIs are formulated from micronized drug particles with aerodynamic particle sizes 2-5μm which is suitable size for depositions in the lungs. FDA guideline on this topic from 1998 was updated to reflect relevant standards and requirements to enhance understanding of suitable development approaches for DPI consistent with the quality by design (QbD) paradigm. DPI applicants be obliged to provide their development and manufacturing procedures according to all regulatory requirements applicable including for design control Q8(R2) and the quality target profile (21 CFR 820.30(c)) along with critical quality attributes for final product (21 CFR 820.30(d)). Stability tests have to performed as recommended by the international guidelines specified in ICH Q1A (R2). The aim of recent study is to present an overview of DPI formulation of ciprofloxacin hydrochloride (CIP) in a carrier free formulation by applying the QbD approach according to the FDA requirements.

MATERIALS AND METHODS: CIP was supplied by Teva Pharmaceutical Company (Hungary). L-leucine (LEU) was obtained from Hungaropharma Ltd.(Hungary). For preparing DPI, 1 g of CIP and different excipients in 10% aqueous ethanol (v/v) were dissolved and the feeding solution was prepared, than subsequently spray-dried using the Büchi Mini Dryer B-191 (Switzerland). The technical tool used for the Risk Assesment was LeanQbD® software (QbDWorks LLC, Fremont, CA, USA). After the physico-chemical characterization (size distribution, morphology, density), we determined the in vitro lung deposition (Andersen Cascade Impactor) and performed stability testing.

RESULTS: The application of LEU to the microparticles induced an enhancement in the aerodynamic behavior based on appropriate size and morphology, and also allows a very fast drug release. DPI with LEU exhibit acceptable aerosol performance for CIP, while maintaining FDA requirement during storage.

CONCLUSIONS: Besides the adequate formula development, this study confirmed that the QbD-guided modern research methodology could be properly used in the early development phase of innovative formulations like DPIs and resulted in a risk-based and effective product development.

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P3/5

Contribution to development of discriminative dissolution method for inhalation preparations

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INTRODUCTION: With an increase in number of generic preparations for inhalation, there is an increased need for new methods for their biopharmaceutical characterization. The only compendial tests available are Aerodynamic assessment of fine particles and Uniformity of delivered dose. There is no official test for dissolution of active

substance which can be highly important, especially for poorly soluble drugs frequently formulated as inhalers [1]. Majority of described dissolution methods for inhalers don`t have discriminating power to detect differences between different formulations with the same API [2].

MATERIALS AND METHODS: This paper describes new method for determining drug dissolution from inhalers. The apparatus employed is based on the modified USP apparatus 5 with flat bottomed dissolution vessel and disc containing polysaccharide gel membrane. Samples were collected using the abbreviated cascade impactor so that dissolved substance originates exclusively from the fine particles fraction. Three commercial products containing beclomethasone dipropionate were tested. Aerodynamic assessment of fine particles was performed using the Ph.Eur. Apparatus E.

RESULTS: Results of aerodynamic assessment were used to calculate the fine particle mass and theoretical maximum of dissolved substance (100%). Obtained dissolution profiles were evaluated using model dependent and model independent methods. The dissolution profiles obtained were best fitted to the first order and Hixon-Crowell model. Dissolution profiles comparison based on the similarity and difference factors calculation (f1 and f2) indicated statistically significant differences among the investigated products.

CONCLUSION: Dissolution method proposed revealed differences in drug dissolution rate from three commercial inhalation products. Good accordance with the first order and Hixon-Crowell dissolution models imply that the main influence of dissolution rate comes from drug particles of inhaler product. Characteristics of the dissolution process employed, including very low dissolution media volume, diffusion through polysaccharide gel membrane, and sample composed of the fine particles fraction, highly mimic in vivo conditions and form good basis for confident biopharmaceutical characterization of preparations for inhalation.

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P3/6

Physicochemical examination of co-milled levodopa containing nasal powders

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INTRODUCTION: Parkinson disease is one of the most frequent neurodegenerative disorder of the central nervous system which is the most efficiently treated clinically by levodopa (LEVO) [1]. Intranasal route as a new approach is an alternative possibility for administration of LEVO in powder form compared to peroral intake [2]. The aim of the work was to select such excipient/additive which is incompatible with the LEVO and help to set the requirements for nasal powder using dry co-milling technology.

MATERIALS AND METHODS: The materials used were the following: levodopa (LEVO; Hungaropharma, Hungary), L-ascorbic acid (Bayer AG., Germany), alpha-cyclodextrin (Sigma Aldrich, Hungary), D-mannitol (Sigma Aldrich, Hungary), hydroxypropylcellulose (HPMC; Sigma Alrich, Hungary), poly(vinyl alcohol) (Sigma Aldrich, Hungary) and polyvinylpyrrolidone (PVP) (Sigma Aldrich, Hungary).

Co-milling was applied by PM 100 planetary ball mill (Retsch GmbH, Germany).

The samples were investigated by following instruments: Mastersizer 2000 (Malvern Instruments Ltd., Worcestershire, UK), Xray Diffractometer Miniflex II (Rigaku Co. Tokyo, Japan), Avatar 330 FT-IR spectrometer (Thermo Nicolet, USA), Mettler Toledo DSC-821e instrument (Greifensee, Switzerland) and Agilent 1100 HPLC (LabX, Canada).

RESULTS: Target size range (5-40 μm) was achieved in each LEVO:additive product. Between of LEVO and additive, hydrogen bond was detected (LEVO:PVP, LEVO:L-ascorbic acid and LEVO:D-mannitol) and eutectic mixture was formed in case of LEVO:L-ascorbic acid mixture. Among the products tested the LEVO:PVP mixture showed the fastest drug release (t10min=65,7 %). It was found that LEVO did not decompose during co-milling process and the quantity of active agent in the products

did not decrease investigated according to accelerated stability test (ICH Q1C guideline).

CONLUSIONS: PVP was selected as additive to prepare the mixture of LEVO:PVP by co-milling technique and this product is suggested for intranasal administration. It may be a new LEWO containing dosage form to ensure fast effect in crisis therapy.

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P3/7

Formulation and administration parameters for the optimisation of nasal deposition pattern of sprayable in situ gelling fluticasone delivery system

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INTRODUCTION: Nasal delivery receives much attention as an attractive route of drug administration. The anatomy and physiology of the nasal cavity are recognized as the most critical factors in drug delivery system design, especially mucociliary clearance that limits drug-to-mucosal surface contact time [1]. However, the crucial parameter for the treatment outcome is drug deposition within the nasal cavity [2]. The purpose of this study is to set the basis for the development of sprayable in situ gelling fluticasone delivery system and to recognise the formulation and administration parameters with the highest impact on nasal deposition pattern.

MATERIALS AND METHODS: Pectin based in situ gelling fluticasone suspensions have been prepared using Tween 80 as a suspending agent and mannitol as a tonicity agent. Sodium hyaluronate was evaluated as potential gel-structuring and bioactive formulation constituent. In situ gelling systems were characterised in terms of suspended particle size (Olympus BH-2 microscope, Japan), rheological properties (Rheometer MCR 102, Anton Paar, Austria), sprayability/droplet size distribution (Malvern Spraytec, UK) and nasal deposition pattern (human nasal cavity model, Koken. Co. Ltd., Japan).

RESULTS: Pectin based in situ gelling fluticasone suspensions have been succesfully prepared. Under formulation and administration parameters employed, appropriate window of droplet size distribution and spray angle was reached resulting in targeted deposition pattern within the nasal cavity.

CONCLUSIONS: Screening studies revealed the parameters to be included in experimental design aiming to elucidate their relation with in situ gelling system properties/deposition pattern. Such an approach potentiates the development of fluticasone in situ gelling system with built-in quality attributes in a cost and time-saving manner.

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P3/8

Preparation and characterization of methacrylate copolymer-based microparticles for intranasal application

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INTRODUCTION: Polymeric microparticles have an increasing importance as drug delivery systems in the field of medicine because of their controlled release properties [1]. Polymeric microparticles can be applied intranasally for the delivery of drugs to reach the systemic circulation or directly the brain tissues [2, 3]. The aim of this study was to prepare and investigate synthetic polymer based microparticles, soluble at the pH of nasal mucosa, ensuring controlled release of meloxicam, a non-steroidal anti-inflammatory drug.

MATERIALS AND METHODS: Eudragit® L30D-55 (Evonik, Germany), the aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate with 30% dry substance was used as a matrix former. Empty and meloxicam-containing microparticles were produced by

emulsification/solvent evaporation method applying spray-drying (Büchi Mini Dryer B-191, Switzerland). In case of drug containing samples, meloxicam was dissolved in dimethyl sulfoxide and the solution was emilsified in the polymer dispersion using high intensity ultrasound (Hielscher UP 200S Ultrasonic processor operating at 200 W, Germany). Particle size distribution, morphology, drug content and structure of microparticles, and in vitro release of meloxicam at the pH of nasal mucosa were determined.

RESULTS: The results revealed that microsized (D90 = 16.8 μm) polymeric particles had monodisperse particle size distribution, suiting the requirements (10-40 μm), and nearly spherical shape in case of meloxicam containing samples. The drug content of microparticles was determined, which was approximately 70%. During the structural characterization of meloxicam containig products, the molecularly dispersed form of drug was experienced, because the charateristic peaks of meloxicam on the X-ray diffractogram and the endothermic peak of the thermoanalytical curve disappeared. In vitro investigation exhibited 70% of dissolved amount of drug in first 15 min at pH 5.6.

CONCLUSIONS: It can be concluded, that Eudragit® L30D-55-based microparticles are suitable for intranasal application, ensuring controlled drug release.

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P3/9

In vitro and in vivo characterization of nasal powder containing nanonized lamotrigin

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INTRODUCTION: Lamotrigine (LAM) as antiepileptic agent is currently used in monotherapy for partial seizures and bipolar disorder by tablet form. Its intranasal powder formulation could offer an alternative administration way, due to the better adhesion and absorption ability through the nasal mucosa. In our previous studies we determined and validated the Design Space of a dry milling method for producing nasal powders that containing nanonized LAM [1]. The aim of present work was the in vitro and in vivo characterization of the optimized nasal powder.

MATERIALS AND METHODS: LAM, a slightly water soluble antiepileptic agent was donated by Teva Pharmaceutical Industries Ltd., Hungary. PVA as water soluble synthetic polymers was purchased from ISP Customer Service GmBH, Germany.

Co-grinding using a Retsch PM 100 apparatus (Germany) was applied for sample preparation. A physical powder mixture was prepared as a reference sample in the same weight ratio: 0.8. After the characterization of the habit and structure, we focused on in vitro and in vivo investigations. The dissolution rate of the final product under nasal conditions were also determined at 267 nm by ATI UNICAM UV–VIS. In vitro permeability testing was performed using a Side-Bi-Side horizontal diffusion cell (Crown Glass, USA). In vivo study of LAM was carried out in Sprague–Dawley rats (n=4). A dose of 550 μg drug per animal was administered into the left nostril. The quantification of the drug content in the plasma and in the brain was performed with a HPLC system.

RESULTS: Co-grinding of LAM with PVA produced a nasal powder formulation with around 100 nm of LAM nanoparticles. In vitro investigations have demonstrated a fast drug liberation of nanosized LAM (100% after 10 min). By the in vivo test in the brain tissues we detected 10 times higher Cmax (12.322 μg/g) for nanonized LAM compare with the physical mixture and 2 times higher drug level compare with the i.v. administration. This high C_{max} value was reached at 3 min by nasal administration compare with i.v. administration where the Tmax was 10 min.

CONCLUSION: We observed correlation between in vitro and in vivo results therefore concluded that the developed intranasal powder containing nanoparticles may be a novel antiepileptic application form of LAM.

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P3/10

Self-emulsifying formulations of vancomycin for ocular delivery – a novel approach to administering moisture-labile water-soluble drugs

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INTRODUCTION: Self-emulsifying drug delivery systems (SEDDS) are water-free dosage forms consisting of an isotropic mixture of oils and surfactants. Following dilution with the aqueous media (lacrimal fluid) with gentle agitation (as occurs with blinking) a fine oil-in-water emulsion is created at the site of administration [1]. Vancomycin is a glycopeptide antibiotic indicated for severe infections caused by Gram-positive bacteria. The substance is marketed as a powder for extemporaneously reconstituted solution for infusion and up to now no ophthalmic dosage form is commercially available [2]. Current project is focusing on the development of ocular self-emulsifying suspension of an instable drug which requires moisture protection during storage. It was previously indicated that SEDDS may be a promising strategy for ophthalmic delivery improving the shortcomings of entirely oil-based systems [1].

MATERIALS AND METHODS: SEDDS carriers were obtained by dissolving Cremophor EL, Tween 20 or Span 80 in Miglyol oil (1% or 5% w/w). Vancomycin was incorporated in SEDDS (1% w/w) by grinding in a mortar (solid particles size < 25 μm). The self-emulsification performance upon dilution with deionized water was evaluated visually. Microscopic images of placebo, vancomycin-loaded and reconstituted SEDDS formulations were obtained using fluorescent microscope (Nikon Eclipse i50, Tokyo, Japan).

RESULTS: The SEDDS suspensions diluted with water were reported to spontaneously form fine emulsions exhibiting an immediate dissolution of vancomycin. Individual systems differ slightly upon two features: reconstitution time and mean droplet size. Preliminary studies revealed that the formulations should meet the requirements for storage stability. The full chemical stability studies are ongoing. The appropriate HPLC analytical methodology has been developed for vancomycin quantitative determination.

CONCLUSIONS: The developed formulations seem feasible and might be further assessed with other methods (e.g. microbial assay). Subsequent research will focus on obtaining detailed formulation characteristics which are indispensable to be determined before proceeding to in vivo testing.

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P3/11

Predicting the biopharmaceutical properties of ibuprofen-loaded cationic nanoemulsion using 3D in vitro corneal model

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INTRODUCTION: Dry eye disease is a multifactorial disease of the ocular surface characterized by instability and increased osmolarity of the tear film, ocular surface inflammation and damage [1]. Current strategies are focused on the development of O/W nanoemulsions since their nanosized lipid dispersed phase can improve the tear film stability [2]. Moreover, cationic nanoemulsions bear the poteintial to increase both, precorneal drug residence time and corneal epithelium related absorption. Current project is focused on the development of ibuprofen-loaded cationic nanoemulsion optimized for its biocompatibility and therapeutic potential using 3D in vitro cell model.

MATERIALS AND METHODS: Nanoemulsions were produced using microfluidizer (Model M-110EH-30, Microfluidics, USA). The oil phase was composed of Mygliol 812, lecithin S45 and ibuprofen, and the aqueous phase of Cremophor EL, low molecular weight chitosan, glycerol and water. Nanoemulsions were characterized in

terms of droplet size and zeta potential (Zetasizer 3000 HS, Malvern Instruments, UK), pH, osmolarity, in vitro release and stability. 3D in vitro model based on human corneal epithelial cells (HCE-T, Rikken, Japan) was used in biocompatibility, mucoadhesion and therapeutic potential screening.

RESULTS: Within this project, formulation and process parameters of nanoemulsion preparation have been optimized. Ibuprofen-loaded cationic ophthalmic nanoemulsions with droplet size of 163,3 ± 0,7 to 185,0 ± 2,1 nm, polydispersity index of 0,11 ± 0,02 to 0,21 ± 0,02 and zeta potential of 16,4 ± 0,6 to 36,5 ± 1,4 mV have been successfuly prepared. Chitosan coating was shown to provide pronounced mucoadhesivity while showing compatibility with 3D HCE-T cell model.

CONCLUSION: This study showed the potential of cationic nanoemulsions to be developed into a value-added delivery platform of ibuprofen for efficient symptomatic and causative dry eye disease treatment.

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Cyclodextrin-Modified Mucoadhesive Polymers as an Enhancer of Ophthalmic Drug Delivery

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INTRODUCTION: Ninety percent of the ophthalmic formulations on the market are eye drops and ointments thanks to their simple administration. These formulations have very low, 2%–5% bioavailability. Steroidal anti-inflammatory drugs are lipophilic drugs; they dissolve very poorly in water. The water solubility can be improved with cyclodextrins (CD).

The aim of this work was to combine the advantages of CD and a mucoadhesive thiolated polymer, thiolated poly(aspartic acid) (PASP-CEA) by the chemical immobilization of CD onto PASP-CEA.

MATERIALS AND METHODS: PASP-CEA was functionalised with 6-deoxy-6-monoamino-β-cyclodextrin (MABCD). The formation of the CD-drug complex in the gels was analyzed by X-ray powder diffraction. The ocular applicability of the polymer was characterized by means of physicochemical, rheological and drug diffusion tests. Osmolality, refractive index, and pH were measured in aqueous solutions of PASP-CEA and PASP-CEA-CD [1]. The drug diffusion profile of PR was determined with a vertical Franz diffusion cell system.

RESULTS: The solubility of PR increased linearly as the CD concentration increased. The X-Ray diffractogram of the formulations showed an amorphous pattern. The osmolality, pH and refractive index of the polymer solution confirmed the ocular acceptability of the formulations.

During the rheological investigations, the PASP-CEA solution displayed a fast solution-to-gel transition in the presence of an oxidant. The immobilization of MABCD on the polymers did not hinder the gelation process.

The complexation of PR with CDs improves PR solubility in aqueous medium. The complexes diffuse in the formulation and can carry the PR molecules through the aqueous mucin layer [2]. The PASP-CEA-CD-PR complex prolonged the drug diffusion through synthetic and improved it through amniotic membrane [3].

CONCLUSIONS: The chemical bonding of MABCD to the PASP-CEA polymer did not change the complexation of the CD with PR, while the hydrogel preserved its mucoadhesion. The diffusion studies indicated that the grafting prolonged the drug release and the best release profile was obtained with the combination of free and grafted CD.

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Formulation of steroid containing eye drops with cyclodextrin derivatives and mucoadhesive preservative system

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INTRODUCTION: For the purpose of increasing the efficiency of the ocular drug delivery, the enhancement of water-solubility and the contact time of the drug are essential [1]. The most commonly used preservative is benzalkonium-chloride (BK). The cornea-cell apoptosis and irritation inducing effects of BK are already published. An alternative additive, like Zn-containing materials, could replace BK, due to the antimicrobial effect of Zn2+-ion [2]. In this work, prednisolone (PR) containing eye drops were formulated with mucoadhesive, preservative zinc-hyaluronate (ZnHA) and PR-cyclodextrin inclusion complex, which approach can be used for the development of innovative eye drop formulations.

MATERIALS AND METHODS: The PR-hydroxypropyl-β-cyclodextrin (HPBCD) and PR-hydroxypropyl-γ-cyclodextrin (HPGCD) complexes were investigated by phase solubility study. The cytotoxicity of the samples was tested on human corneal epithelial cell lines (HCE-T) by MTT-test and impedance-based cytotoxicity assay. The permeation of PR was studied in vitro using dialysis membrane and HCE-T cell line. The mucoadhesive force was measured by tensile-test. The antimicrobial effectiveness was tested by a standard method of the European Pharmacopoeia (EP).

RESULTS: PR-cyclodextrin complex formation can be assumed according to the phase-solubility test. The determined apparent stability constant of PR-HPGCD is higher than in the case of the PR-HPBCD inclusion complex. The data of cytotoxicity test on HCE-T cell lines are acceptable, such as the microbiological stability, which meets the requirement of EP. The in vitro drug-permeability assay shows the increased penetration of PR through the dialysis membrane and HCE-T cell line. According to the tensile-test, the mucoadhesive properties of the ZnHA containing samples could prolong the therapeutic effect on the eye surface.

CONCLUSION: Considering the results, it can be stated that our work could be an innovative approach for the development of novel, steroid containing, mucoadhesive, properly preserved ophthalmic solutions with increased bioavailability.

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Evaluation of mucoadhesive properties of ocular lubricants containing hydroxypropyl guar gum and chitosan

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INTRODUCTION: Incorporation of mucoadhesive polymers is one of the most used strategies to prolong the residence time between the ocular vehicles/lubricants and ocular surface. Improvement in residence time aims to decrease the frequency of the lubricant administration [1]. The aim of this study was to develop ocular lubricants with appropriate physicochemical and mucoadhesive properties containing hydroxypropyl guar gum and chitosan.

MATERIALS AND METHODS: Compounded ocular lubricants containing HP-guar (HP GG; 0.25 %, 0.5 %, 1.0 %), medium molecular weight chitosan (MCS; 0.5 %) and their combination HP GG 0.25 %/MCS 0.5 % were investigated. The commercial eye drops Systane® Ultra Lubricant (SU) containing HP GG were also tested. The formulations were evaluated for clarity, pH and osmolality. The viscosity measurements were performed using a rotational rheometer at 20 and 34 °C (after addition of the simulated tear fluid-STF) in a ratio of 40:7. Potential mucoadhesive properties were investigated using turbidimetric and mucin-particle method [2]. The mucoadhesiveness of the polymer solutions was estimated by calculation of mucoadhesion index [3].

RESULTS: The pH and osmolality were within the acceptable range for ophthalmic preparations. All formulations were clear, except formulation with 1.0 % HP GG. The formulation containing combination of polymers (HP GG/MCS) showed significantly higher viscosity (49.6 mPa•s) than viscosities of formulations with single polymer (7.4 mPa•s for HP GG and 6.8 mPa•s for MCS). After dilution with STF, a 2-fold increase in viscosities of formulation with 0.25 % HP GG and SU

drops were observed. The both turbidimetric and mucin-particle method revealed that combination of MCS and HP GG had synergistic effect on mucoadhesion of this solution. Mucoadhesion index of HP GG/MCS formulation (63.3 %) was higher than for the vehicle containing only MCS (31.3 %).

CONCLUSION: The formulation containing combination HP GG 0.25 %/MCS 0.5 %, may be considered as a promising ocular lubricant with optimal viscosity and mucoadhesive properties. It can be concluded that HP GG and MCS show positive synergistic effect and addition of HP GG resulted in better mucoadhesive properties of this ocular lubricant.

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P3/15

PEG-ylated parenteral nanoemulsions: employing the experimental design in selecting optimal formulation and critical process parameters

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INTRODUCTION: Parenteral nanoemulsions (NEs) containing PEG-ylated phospholipids (PEG-PLs) can increase target site concentration of the incorporated active substance by increasing circulation time of the oil droplets. The aim of this study was to develop PEG-ylated NEs (PEG-NEs) with the smallest droplet size and size distribution using the experimental design strategy.

MATERIALS AND METHODS: PEG-NEs were prepared by high pressure homogenization method at 50°C. Oil phase (soybean oil, benzyl alcohol, medium chain triglycerides, soybean lecithin and butylhydroxytoluene) was added to water phase (glycerol, polysorbate 80, sodium oleate and highly purified water) and homogenized with high-pressure homogenizer (EmulsiFlex-C3, Avestin Inc., Canada). PEG-PL – PEG2000-DSPE/PEG5000-DPPE, was added to the oil or water phase at 0,1%/0,3% concentration. A D-optimal factorial experimental design was used to estimate main and interaction effects of two formulation factors (PEG-PL type and concentration) and two process variables (homogenization pressure – 500 bar/800 bar, and number of cycles – 5/10/15) on NE droplet size (Z-Ave) and polydispersity index (PDI). To fit the experimental data, the first-order polynomial model was applied. Results obtained for each response were statistically evaluated using Design-Expert software (Stat-Ease Inc., MN). Zeta potential (ZP) was also measured in order to assess the stability of PEG-NEs.

RESULTS: Concordant with applied experimental design, 25 NE formulations were prepared. Mean droplet size of all NEs was in the range of 105–172 nm, with PDI below 0.2 and ZP about –40 mV, suggesting that developed NEs were suitable for parenteral use. Experimental design results showed that generated models for Z-Ave and PDI of NEs were significant ($p<0.05$), indicating that these responses were well described by the proposed models. Further, not only investigated factors alone, but also their interactions were shown to significantly affect NE characteristics.

CONCLUSIONS: This study shows the usefulness of D-optimal factorial design in NE development. Both investigated PEG PL types and concentrations homogenized for 10 cycles at 800 bars showed the best results and were selected for further NE research.

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P4- BUCCAL DELIVERY AND PRINTING TECHNOLOGIES

P4/1

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

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

MATERIALS AND METHODS: PVP K25 and Polysorbate 80 was used for setting of the viscosity and surface tension of the ink according to 32 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.

RESULTS: The results revealed that the viscosity plays considerably higher role in the ink behaviour than surface tension. The highest dose/printing time was achieved with inks with high viscosity and surface tension, however this combination acts negatively on printing accuracy since the drop formation is not balanced with the trigger signal. Low viscosity promotes the ink penetration into the substrates which acts positively on the printing and drying speed but affects the printing pattern negatively especially in highly porous substrates.

CONSLUSION: 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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P4/2

Biocompatibility examination of 3D printed implants manufactured by different base polymers and side chains

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INTRODUCTION: 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 by fused deposition modelling 3D printing technique at the University of Claude Bernard, Lyon.

MATERIALS AND METHODS: Our aim was to determine the biocompatibility of the implants because implanted devices must be biologically compatible with the tissues. The aim is to maximalise the benefit and minimize the risk [1]. Biocompatibility can be examined by MTT cell viability test and biofilm formation [2-3]. 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: The implants were not only made up by different polymers but eight different side chain was connected by a chemical reaction to the base frame. More than 45 different implants were examined. Our results indicate how this modification effect the cytotoxicity and biofilm forming ability of the implants.

CONCLUSIONS: Based on the results we can select the best implants which are appropriate to further examinations.

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P4/3

The 3D-FDM printability assessment in terms of pharmaceutical polymers/polymeric blends

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INTRODUCTION: The three dimensional printing (3DP) in the pharmaceutical domain constitutes an alternative, innovative approach compared to the conventional production methods. With roots in engineering, it was considered for pharmaceutical applicability based on the need to improve product quality and enable therapeutic personalization. Fused deposition modelling (FDM), is a simple, cost-effective 3DP technique, however the FDM apparatuses are adapted for restricted number of commercially available filaments, that are either non-biocompatible or yield limited dissolution kinetics. The transfer of pharmaceutical polymers to FDM desktop printers is possible [1, 2], but the technological barriers are yet to be established. The study set to define the requirements of the FDM printability, using as technical support custom made, pharmaceutical polymer based filaments. The therapeutic suitability of the 3DP tablets was assessed with regards to assuring a once a day posology.

MATERIALS AND METHODS: Carvedilol was used as a model API. Several retard polymers with known applicability in hot melt extrusion (HME) were tested, the actual screening process constituting the FDM printability. Unassociated polymers were compared with polymeric blends in terms of productivity. The technological process implied the use of FDM (Craftbot Plus, Craftunique, Hungary) coupled with HME (Haake Minilab, Thermo Fisher Scientific, USA). Printability was defined by means of thermal, rheological and mechanical measurements. The resultant 3DP tablets were tested for API crystal form and in vitro dissolution kinetics.

RESULTS: Results showed that FDM printability is multifactorial, with brittleness, melt viscosity and flexibility as primary limitation factors. Up to 65000 Pa*s (at 0.1 rad/s angular frequency) complex viscosities can be transferred to FDM, however, the upper viscosity limits require optimal flexural modulus values for productivity. The 3DP tablets released the API in an extended rate, comparable to the Coreg CR (carvedilol phosphate) dissolution kinetics.

CONCLUSIONS: Manufacturability and quality are dependent upon printability. Polymeric blends, with printability improvement, enable broader processing conditions. HME+FDM shows potential of consistent quality by the reduction in critical material attributes and process parameters.

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P4/4

Optimization of printing process parameters for printlets fabricated by FDM printing

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INTRODUCTION: Fused deposition modeling (FDM) is a method of filament deposition that involves successively melting and cooling thermoplastic materials [1]. Three-dimensional printing (3DP) technology is based on computer designs and it is an effective strategy to overcome some problems of conventional pharmaceutical forms, such as poor dose flexibility [2].

MATERIAL AND METHODS: Firstly, filament with Hydrochlorothiazide, Hypromelosis and Polyvinyl Alcohol (PVA), at a weight ratio of 10:10:80, was made in Filabot EX2 Filament Extruder (Filabot, SAD). The selected size (X=10 mm, Y=10 mm and Z=3.885 mm) and shape of the printlets were designed with UltimakerCura 3.2.1 software. Printlets were fabricated with the previously drug-loaded filaments using a fused-deposition modeling (FDM) 3D printer Ultimaker 3 (Ultimaker B.V, Netherlands) with infill 100% and line pattern. During printing, printing temperature and speed were varied according to D-optimal design (Design Expert 7.0.0, StatEase.). The temperature varies from 180 to 250 degrees, and

printing speed from 50% to 100%. Total number of experiments were 11.

RESULTS: Prerequisite of successful and reproducible printing is consistent flow through the FDM 3D printer nozzles. Commercial filaments were not used during the experiments and this led to the clogged nozzles if the temperature of printing was not appropriate, so the nozzles must be cleaned more often than usual. The best printlets were fabricated when printing temperature was 215 degrees and printing speed 50%. With other temperature and speed values, printing was unsuccessful. The average weight of the printlets obtained under the best conditions was 0.1805 mg, average length was 9.57 mm and average thickness 3.7 mm. The tablet strength data show values between 72 and 140 N.

CONCLUSION: In this study, we represent that printing temperature and speed are critical parameters that enable successful fabrication of printlets. It is necessary to find optimal process parameters for every type of filament, where experimental design can be useful method for defining parameters of interest.

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P4/5

3D printing of tablets for the treatment of cardiac arrhythmias – from filament to tablet

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INTRODUCTION: Fused deposition modeling (FDM) is an extrusion-based 3D printing technique easily accessible, versatile, low-cost and shows good potential for fabrication of single-unit dosage forms [1]. FDM allows variation of the type, dose, and distribution of the active ingredient as well as the size, shape, geometry, and density of the final product [2]. Because of the increasing interest for FDM in the pharmaceutical research area, the development and fabrication of filaments with active ingredient have become very important. Widely used technique for incorporating the active ingredient into the filament is hot-melt extrusion (HME). The aim of this paper is to produce filaments containing active ingredient and 3D printing of the tablets using FDM technology.

MATERIALS AND METHODS: Mixtures of dronedarone hydrochloride (DNR), poly(ethylene glycol) (PEG) and poly(vinyl alcohol) (PVA) filament in various proportions were used. The mixtures are prepared as a mixture of powders and as a solid dispersion. Melt flow rate of mixtures and thermogravimetric analysis of DNR were performed. The filaments were produced by HME. Diameter of prepared filaments was measured and swelling test was performed. Thermal properties of filaments and prepared mixtures were examined using differential scanning calorimetry. Prepared filaments were used for 3D printing of tablets by FDM. An in vitro drug release assay was performed from the obtained tablets. The content of dronedarone in filaments and tablets was determined using UV/Vis spectrophotometry.

RESULTS: The results indicate that the 10% PEG-containing solid dispersion mixture has the highest melt flow rate. The filament prepared from a solid dispersion containing 10 % PEG has the most straightforward structure; it shows the slightest deviation from the target filament diameter (1.75 mm). The compact structure of the tablet obtained from the filament contributes to a uniform in vitro release of the DNR from matrix during 24 h. It also shows the slightest deviation from the targeted DNR content in the tablet.

CONCLUSION: According to all observed properties, a blend containing 10% PEG, 10% DNR and 80% PVA filament is most appropriate for HME and FDM tablet printing.

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P4/6

Effectiveness of a lipid-based subgingival system for the treatment of periodontal disease

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INTRODUCTION: Periodontitis is a chronic inflammatory disease affecting the gingiva. Anaerobic bacteria have a major role in its development. Being the most prevalent cause of adult tooth-loss without a properly effective therapy, a convenient method is needed for the treatment of the disease. The aim of the recent research was to create a subgingivally employable lipid based delivery system for the local delivery of antibiotics.

MATERIALS AND METHODS: For the preparation of the formulations lipid bases, waxes as structure-building components, a surfactant, polymers and different antimicrobial agents were used. Various methods were used to find the optimal composition of the systems. The physical properties were characterized by differential scanning calorimetry, wettability, swelling and degradation measurements and cone penetration tests. Drug release measurements and antimicrobial tests were carried out to evaluate the effectiveness against oral pathogen bacteria and to assess the possibility of sustained release.

RESULTS: Results of DSC measurements show that at higher wax concentrations, total melting of the systems can be avoided, and a soft but coherent structure may be present at body temperature. According to the results, the concentration of the surfactant may not have remarkable influence on the melting point of formulations.

Higher concentrations of the surfactant increase the wettability and decrease the consistency of the systems, while increasing the amount of the wax does the opposite.

Swelling and degradation measurements indicate that a minimum concentration of wax is needed and the higher the concentration of the wax the lower the degree of swelling and slower the degradation.

The results of the drug release tests show that with a higher concentration of wax, sustained release of drugs and, together with the results of an antimicrobial study, a one-week antimicrobial effect against oral pathogen bacteria may be possible.

CONCLUSION: The optimal concentration of the components allows sustained release of antibiotics, which may provide a long-lasting antimicrobial effect and can contribute to the establishment of an effective and convenient therapy.

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P4/7

In vitro – in vivo characterization of nanoparticulate mucoadhesive polyherbal gel designed for the treatment of periodontitis

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INTRODUCTION: Periodontitis is a chronic inflammation of the teeth supporting tissues, involving endogenous collagenolytic enzymes, especially matrix metalloproteinase 8 (MMP-8) [1]. Topical application of active principle directly into the periodontal pocket represents a satisfactory approach, presents many advantages and involves the use of a controlled release device with mucoadhesive properties [2]. Phytoconstituents as flavonoids, catechins, saponins, tannins, essential oils can have a high anti-inflammatory and antioxidant potential and they could exert an effect of inhibiting MMP-8 activity at the periodontium level.

MATERIALS AND METHODS: The purpose of this work was to formulate a nanoparticulate mucoadhesive polyherbal gel (NMPH gel), based on Echinacea purpurea, Camelia sinensis, Filipendula ulmaria and Calendula officinalis extracts and to evaluate in vivo efficacy regarding clinical parameters, histopathology and immunologic profiles (serum and salivary levels of MMP-8). The designed NMPH gel formulation consisting

of Carbopol 940 and Kolliphor P407 was prepared and evaluated regarding the rheological properties and in vitro adhesive capacity (assessed by measuring the time of detachment of the sample from a synthetic membrane). The total polyphenolic content of the polyherbal extract was estimated using Folin-Ciocalteu reagent and the content of epigallocatechin-3-gallate was analysed by HPLC coupled with Mass Spectrometry. The in vivo testing of the NMPH gel was performed using an experimental model of induced periodontitis in rats, by placing the ligatures around the inferior incisor.

RESULTS: The studied NMPH gel showed rheological and in vitro adhesion properties suitable for application in the periodontal pocket that can provide adherence to the gum for a prolonged period of time, ensuring an increased concentration in total polyphenols at this level. The experimental results showed that topical application of designed NMPH gel reduced the local inflammatory response induced by periodontitis, led to clinically and histopathologically healing of gingival lesions and determined a decrease in serum and salivary levels of MMP-8.

CONCLUSION: The results suggest that the prepared NMPH gel may be favorable for topical application in periodontal therapy.

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P4/8

Preparation of mucoadhesive alginate films – comparison of solvent casting and freeze thaw method

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INTRODUCTION: Mucoadhesive films are relatively new drug dosage form, which might be applied to the oral, buccal, gingival and vaginal mucosa. They are designed for drugs characterized by poor absorption or having local action. Properties of films are significantly affected by method of preparation and type of polymer [1, 2]. Sodium alginate (ALG) is natural, non-toxic and biocompatible polymer from polysaccharides group. Due to its unique properties – gelation, swelling and mucoadhesion – ALG is a valuable excipient used to design various drug dosage forms [3]. In order to improve polymer properties, cross-linking using different methods might be conducted. Novel method of ALG gelation includes freeze-thaw technique [4]. In this work, ALG films were prepared by solvent casting and freeze thaw method and the influence of preparation technique on the properties of obtained formulations was examined.

MATERIALS AND METHODS: In the first step, mixtures containing different concentrations of ALG (1%, 2%, 3%) and glycerol (used as plasticizer) were prepared and poured into plexiglas moulds. In the freeze thaw method freezing at -20°C for 18 h and thawing at room temperature for 6 h, for three consecutive cycles were conducted [5]. After drying, films were cut into pieces of 2×3 cm. Obtained formulations were evaluated for size, morphology, thickness, mechanical properties and swelling degree. Mucoadhesiveness of the films was evaluated using bovine buccal mucosa to imitate in vivo conditions.

RESULTS: ALG films prepared using both methods were characterized by weight, size, and thickness uniformity. However, films formulated by freeze thaw method possessed better mechanical, swelling and mucoadhesive properties.

CONSLUSION: Designed ALG films fulfill the criteria for mucoadhesive formulations and seem to be promising dosage form for local drug administration.

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Formulation of an innovative buccal mucoadhesive drug delivery system with sodium alginate polymer film

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INTRODUCTION: Mucoadhesive systems such as oral mucoadhesive films have an increasingly greater role in the pharmaceutical industry. These systems make the application easier for the patients because patients do not have to swallow them. It is a very important viewpoint, for example, in the case of children or persons who have a swallowing problem. Another advantage of these drug delivery systems is that they do not have a first-pass effect in the liver because active substance absorption takes place from the buccal mucosa, so it enters the systemic circulation. The current project is focusing on preparing oral mucoadhesive films, which are suitable for binding to the buccal mucosa and for providing the absorption of the active substance.

MATERIALS AND METHODS: Sodium-alginate was used to make a polymer film. This film was made in 2, 3, 4 w/w% concentrations with distilled water. Later the other polymer solution contained glycerol. Glycerol was used in 1, 3, 5 w/w% as plasticizer in the polymer films. The formulation was made in 2 steps. On the first day we prepared the polymer solution from sodium alginate and distilled water and mixed it with 80 rpm. The following day we added glycerol and homogenised and moulded it in a rubber ring. The rubber ring contained 8 g and 10 g of polymer solution. The dried, ready polymer films were investigated, the thickness of the films was examined with a screw thread micrometer and tensile strength was tested with a device and software developed in our Institute (Szeged, Hungary).

RESULTS: The investigation revealed the 4w/w% sodium-alginate polymer films had too much viscosity and were easily broken. When we used glycerol, the films were flexible. The results showed that the plasticizer has a great role in the structure of polymer films. The strength force of the polymer films which contained glycerol was lower but their thickness was higher than without glycerol.

CONCLUSION: In the case of a high sodium-alginate concentration, the films are too fragile and have greater thickness. When using a high glycerol concentration, the films are very flexible and thicker than in the case of a high sodium-alginate concentration. The optimal structure was obtained by using 3w/w% sodium-alginate and 3w/w% glycerol.

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Structural and thermoanalytical analysis of innovative, chitosan based mucoadhesive films

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INTRODUCTION: Nowadays, mucoadhesive buccal films are in the foreground because they are easy to apply, and with this formulation we can avoid the first pass effect, which causes that a lower amount of active ingredient can reach the same effect. Our aim was to examine the structure and the thermoanalytical properties of the films.

MATERIALS AND METHODS: During the formulation of mucoadhesive films, we used chitosan (CH) as the polymer basis of the film. Ascorbic acid (AscA), which provided the acidic pH, besides its permeation enhancer properties, was used in different concentrations (2-5%). We compared the AscA effects on the properties of these films to films made with acetic acid (AA). Glycerol (Gly) was used as a plasticizer. The films were formulated by the solvent casting method. We examined the free volume of the films with positron annihilation lifetime spectroscopy (PALS), and the Fourier transform infrared spectrometer (FTIR) spectra give us useful information as well. The thermoanalytical examination includes TG-MS and DSC measurements.

RESULTS: The PALS and the FTIR spectra show us that the higher amount of AscA cannot build into the structure of the films, the free volume increases, which is confirmed by the FTIR spectra. We detected the thermoanalytical curves of the main substances and the films, which gives us further information about the structure and the thermal degradation.

CONCLUSIONS: The optimal AscA amount is the lower concentration when the dissolution is provided by the acidic pH, but it still can build into the structure of the films.

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P4/11

Design, Development and Characterization of Chitosan Film as Effective Oral-Macromolecule Delivery System Using New Multifunctional Plasticizer

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INTRODUCTION: Nowadays, numerous bioactive proteins and peptides are going through clinical trials and more than 30 have been approved by the FDA for commercialization [1]. However, the transportation of protein drugs in the body is limited because of their high molecular weight and to their short life-time due to immune response and enzymatic degradation [2]. The use of chitosan as a delivery system may improve the oral bioavailability of proteins via the protection against the GI environment and ensure appropriate residence time at the absorption site due to its mucoadhesive properties [3]. Citric acid (CA), may serve as solubility enhancer, plasticizer, permeation enhancer and also inhibits intestinal serine proteases [4].

MATERIALS AND METHODS: Chitosan 80/1000 (Heppe, Germany), acetic acid (AA) and CA were used as solubility enhancer, glycerol, propylene glycol and polyethylene glycol were used as plasticizers, mucin as reagent for the mucoadhesive test and all other used reagents were of analytical grade. Chitosan films were prepared by dissolving the polymer (2% w/v) prepared with the use of acetic acid (2% v/v) as prescribed by Liu et al [5] as reference and with the use of citric acid (2-7 w/v%). The solutions were cast onto Teflon surface and then dried at room temperature for 24 h. The minimal film forming temperature of the films was investigated with a Rhopoint Rhopoint, UK, the hardness and mucoadhesive properties were measured with a self-developed texture analyzer.

RESULTS: The results revealed that CA is an effective solubility enhancer and plasticizer for chitosan, which produces thicker but more flexible and adhesive films in comparison with AA based chitosan films.

CONCLUSION: It could be concluded that CA is a novel multifunctional plasticizer for chitosan, to develop oral films or drug layering/coating of a solid dosage forms of macromolecules.

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P4/12

Quality By Design Approach for Optimizing The Formulation And Characterization of Prepared Buccal Films

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INTRODUCTION: Quality by design (QbD) is a systematic approach to optimize pharmaceutical preparations and to improve the control over and the quality of the production process. The quality by design approach consistently yields a product with desired characteristics and built in quality [1]. The aim of the study is to optimize the characterization results of the prepared buccal film formulations with QbD.

MATERIALS AND METHODS: Chitosan (1% w/v), sodium alginate (1% w/v) and carbopol (0.5% w/v) were used as polymers in combination and individually. Glycerine, PEG 400 and propylene glycol as plasticizing agents are mixed with the polymers at different ratios (5%, 10%, 15%, 20% w/v). Buccal film formulations were prepared by using solvent casting technique [2]. The films were characterized by using Critical Quality attributes (CQA's), moisture loss, thickness, uniformity of weight, and swelling studies. In these studies, Formrules V 3.32 were used as commercial artificial intelligence software tools to obtain a film formulation with optimum characterization.

FormRules V 3.32 is a data mining software package developed by Intelligensys Ltd. that makes use of the neurofuzzy logic as its basic technology [3].

RESULTS: The optimal formulations, provided by the FormRules software, contain 1% chitosan as polymer and 5% PEG 400 as plasticizer. The best match between program results and prepared formulations is F5-coded (1% chitosan and 5% PEG 400) formulation.

CONCLUSION: This work shows that QbD approach studies, using CQA's and especially Statistical tools are very helpful to achieve a greater understanding for formulations

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P4/13

Oral thin films dissolution testing device

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INTRODUCTION: Oral thin films are relatively new oral formulation for drug delivery. Fast acting and avoiding first pass metabolism is the main advantage over the conventional oral route formulations. There is still a lack or analytical methods to sufficiently characterize the dissolution differences between films. Because the films are fast dissolving conventional dissolution methods that can be found in pharmacopeias are not suitable, due to its large volume and turbulent media flow. The main purpose of this study was to develop a better method that can give repeatable and discriminatory results, even for small changes in the film formulation.

MATERIALS AND METHODS: Dissolution system consisted of double chamber flow through cell separated by a membrane. In the donor chamber a film was placed and firmly fixated by the edges of the flow cell. A constant hydrostatic pressure was applied to the flow cell, provided by a custom made constant leveling device. Dissolution media was drained through the donor chamber and the acceptor chamber, causing the dissolution of the film formulation. Media used was circulating in a closed loop trough the chamber until the film has dissolved completely. Eluted media from the flow cell was sampled and analyzed using UV-VIS spectroscopy.

RESULTS: Advantage of presented method compared to the other flow through film dissolution system is in wetting of the film from both sides during the dissolution process. Sigmoid curve of the dissolution rate was observed. Swelling phase of the dissolution is visible from the result. System variables such as media flowrate trough the acceptor chamber and donor chamber pressure were varied to show their impact on dissolution process. It was found that the system is robust because the most vital variables are the one that can be easily controlled. Wetting of the film from both sides was found to be an important factor affecting the dissolution process.

CONCLUSION: A new dissolution method for oral thin films was presented. Main method advantage is that the film is wetted from both sides during dissolution process and it was shown to give a discriminatory result. It is a promising new tool for researches to evaluate their film formulations.

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P5- ORAL CONTROLLED DELIVERY

P5/1

Exploring the usability of modified gelatin films for preparation of gastroresistant soft capsules

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INTRODUCTION: Incorporation of enteric properties into the shell of gelatin-based capsules is a challenging task. Although there are patent applications describing modified shell compositions, there is still lack of detailed description of such approach in the scientific literature. The following work is a continuation of previously published studies [1, 2], aimed for investigating and describing the possibilities of preparing gastroresistant soft gelatin capsules, by incorporation of acid-resistant substances into the shell material.

MATERIALS AND METHODS: Several gela-

tin-based film compositions were obtained, using various acid-insoluble polymers and commercial mixtures intended for enteric coating of tablets: Aquacoat CPD (FMC Biopolymer), Eudragit L30 D-55 (Evonik), Opadry Enteric (Colorcon). The gelatin-polymer compositions have been proved to be resistant to disintegration in acidic media [1, 2]. Microscopic (optical, AFM) and mechanical analyses were performed. Selected compositions were modified with addition of carrageenan, gellan or gum arabic. Such modified films were investigated in terms of pH, viscosity and mechanical properties. Soft capsules, with the shell composed of gelatin and CAP, filled with pigment in MCT oil, were prepared and subjected to disintegration test.

RESULTS: The results show good homogeneity of obtained film compositions. Mechanical study shows alteration of elastic moduli and mechanical strength of the films by addition of the secondary gelling agents. Also adhesion properties of the films have been enhanced by addition of co-gelling substances. The obtained soft capsules proved to be resistant to disintegration in acidic media for 2 h. The acid-phase of the test was followed by test at pH 6.8, in which all capsules disintegrated within 15 min.

CONCLUSIONS: Polymer films can be prepared with use of the investigated compositions. The physical properties of the films can be easily modified by addition of secondary gelling agents, to suit the requirements of soft capsule manufacturing process. Using several compositions, it is possible to form soft capsules resistant to disintegration in acidic media.

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P5/2

Development and characterization of modified-release capsules based on hot-melt technologies

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INTRODUCTION: 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 [2]. PEGs, semisynthetic glycerides, fatty acid and alcholos and their conjugates are favoured to be used as thermoplastic or meltable materials.

METHODS: Fine grade of ethylcellulose, Gelucire 50/13 and cetostearyl alcohol in their powder forms were mixed with model drugs (paracetamol-ACP, metronidazol-MNZ and diclofenac sodium-DS) and filled into capsules. The filled capsules were heated at 63°C to create monolithic lipid matrices. DSC, TG, NIR pXRD was used to characterise the lipid matrices beside dissolution tests and texture analysis.

Custom made jacketed dispensing vessel created to melt, disperse and foam the PEG and stearic acid based dispersion of metronidazol. Hot foams formed monolithic matrices in the capsules. Foam cell characteristics and cell size distribution were investigated using SEM. Floating time and dissolution tests with texture analysis measurements were conducted to test in vitro buoyancy.

RESULTS AND DISCUSSION: By in situ matrix formation, solid solution of DS was formed based on pXRD and DSC measurment, while ACP and MNZ remained partially in their undissolved forms. Thermal analysis confirmed thermal stability of the materials. Prolonged dissolution was achived for all API following First-order kinetics. Softening of the lipid matrix was only when only Gelucire was used with DS.

Foaming of MNZ dispersions resulted in decreased density namely from 1.22-1.28 g/ml to 0,77-0,92 g/ml. Stearic acid decreased erosion and improved hardness. SEM pictures showed closed-cell systems with some interconnected cavities, sizes were in the range of 68 and 260 micron. Labrasol and stearic acid ratio was found to determine the dissolution time, ranging from 7 hours to more than 10 hours.

CONCLUSIONS: Hot-melt techniques are successfully provide opportunities to create swellable or erodible lipid matrices with targeted release profiles. Lipid matrices can be formulated without

filling liquid dispersion into capsule shells. Fast and efficient foaming of molten and viscous materials could be used to prolong drug release and gastric residence time.

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P5/3

Enteric film coating of capsules with freeze-dried fecal supernatant in Clostridium difficile infection

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INTRODUCTION: The increase of Clostridium difficile infection (CDI) over the last 15-20 years raised to an epidemic proportion, and the cases were found less sensitive to the applied antibiotics. One of the most successful alternative methods of the therapy is the fecal microbiota transplantation (FMT), which was first reported in the 4th century in China against food poisoning or severe diarrhea. The first scientific approach of administration against CDI was only carried out in 1983 in form of an enema. Later it was confirmed, that fecal infusion via nasogastric tube can be more effective [1]. Increasing the patient compliance, our experiments aimed to find more convenient administration methods of this therapy, such as enterosolvent capsules filled with freeze-dried fecal supernatant.

MATERIALS AND METHODS: The freeze-dried fecal supernatant, which was obtained from healthy donors, was filled in '00' size capsules. Using a prefabricated capsule holder dip coater template and multiple immersing technique, the surface of the capsules was coated by different proportion of Eudragit® L30-D55 and triethyl-citrate dispersion. After proper drying an enterosolvent film coating was formed on the capsules.

RESULTS: According to the results of dissolution tests, less than 5% of the capsule content was released in acidic medium, then the release was completed after changing the medium to phosphate buffer. After getting ethical permissions, administration to humans in co-operation with the Department of Infectology, successful therapy of the CDI was carried out.

CONCLUSION: Our experiments are promising in the field of CDI, yet there are a lot of technological optimization tasks to solve in the future. Patients found this type of administration much more convenient than the nasogastric infusion, which encourage us to continue our research.

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P5/4

API - excipient interaction studies in solid matrix systems

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INTRODUCTION: The solid dosage forms are still the most preferred types of medicines in the pharmaceutical market. One of the current challenges for the pharmaceutical industry is to provide matrix systems with variable properties regarding to the individual patient needs. To fulfil this personalized medicine related request a novel approach of pharmaceutical design may be applied with a more detailed investigation of physico-chemical property-based interactions between the drug and the applied excipients. The main aim of this research work is the better understanding of these interactions and fulfilling the requirements of the 'Functionality related properties of materials' concept of Quality by Desing.

MATERIALS AND METHODS: The binary drug-excipient systems were produced by a Specac hydraulic press (Specac Inc, UK) with 1, 3 and 5 tons compression force. The effect of the interactions on the surface free energy of mixtures were determined with an optical contact angle tester (Dataphysics GmbH, Germany). FT-IR and NIR measurements were applied for the exact determination of the nature of interactions. The influence on dissolution and drug liberation was examined with a custom-made dissolution equipment.

RESULTS: The results revealed that the determination of surface free energy may be a good in-

dicator of the different kind of drug-excipient interactions. The spectroscopic results proved the presence of hydrogen bonds in some matrix systems. As it was expected, the strength of the bonds increased with the increment of the applied pressure. The dissolution studies confirmed the influence of bond-strength on both the drug liberation speed and quantity of liberated drug.

CONCLUSION: According to the above-mentioned results, it can be declared that in addition to the physico-chemical properties of the drug delivery systems the underlying chemical interactions between API and excipient also play a vital role in the drug liberation process. Regarding to more efficient drug design and computational modelling the importance of these interactions is highlighted.

P5/5

Comparison of hydrophilic polymers functionality in formulation of mucoadhesive matrix tablets

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INTRODUCTION: The aim of this study was to examine the functionality of hydrophilic polymers with mucoadhesive properties in formulation of matrix tablets with modified release of propranolol hydrochloride [1]. Swelling and erosion of hydrophilic matrices may affect both release rate and mucoadhesive properties.

MATERIALS AND METHODS: The hydrophilic matrix tablets were prepared by direct compression method using hydroxypropylmethylcellulose (HPMC), polyethylene oxide polymer (PEO) or carbomer in varying amounts (20 or 60%). Mucoadhesive strength was measured on the modified weight scale by using samples of the porcine gastric tissue. Swelling and erosion studies of matrix tablets were analyzed and propranolol hydrochloride release rate was determined in a reciprocating cylinder apparatus (with or without the presence of the gastric tissue) for 210 minutes.

RESULTS: Matrix tablets formulated with 60% of PEO polymer have had the highest degree of mucoadhesion (~ 500 N/m2) leading to prolonged adhesion of tablets to the tissue through the dissolution test. Tablets with 60% of HPMC absorbed the highest amount of water (308% of the initial tablet weight) and had the slowest erosion rate (2,98%/hour). Comparative analysis and modeling of dissolution profiles demonstrated that propranolol hydrochloride release rate was reversely proportional to the swelling rate, and tablets with 60% HPMC had the slowest drug release rate.

CONSLUSION: Matrix tablets formulated with 60% of PEO or HPMC are characterized by high swelling capacity and limited erosion which leads to the high degree of mucoadhesion and sustained propranolol hydrochloride release. These findings are a good basis for the further development of mucoadhesive delivery systems.

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P5/6

Formulation of a multiple oral dosage form containing BCS IV group API and natural polymers as excipients

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INTRODUCTION: The aim of this study is acyclovir (AC), API with problematic pharmacokinetics. Oral doses of AC range from 200 to 800mg every 4 hours for 5-10 days, considering unconvinient from the perspective of patient's compliance. The reason is low bioavailability due to low solubility, low permeability and short retention time of dosage form in the specific part of GIT [1].

Natural polymers currently researched for the development of novel drug delivery systems, such as mucoadhesive, control drug release, dosage form retains in the stomach for longer period of time, what helps to improve bioavailability and reduce drug wastage [2].

MATERIALS AND METHODS: Microcapsules were prepared by the phase separation (coacervation). Polymers used for the encapsulation of AC were gelatin and pectin; glycine and glutaraldehyde for crosslinking process.

Powder containing AC and lactose was wet massed with the psyllium mucilage dispersion and screened through a sieve (0.84 mm). Psyllium mucilage was extracted according to Sharma and Koul's method [3].

Prepared microcapsules and granules were filled in hard gelatin capsules; each capsule contained 200mg of AC.

Dissolution tests were performed with Basket apparatus in simulated gastric fluid (pH 1.2) without pepsin. Samples were withdrawn every 5 minutes for 2 hours and analysed for AC content spectrophotometrically at 255nm.

RESULTS: In the first 45 minutes, the cumulative release of AC was 37,18% from microcapsules and 80,23% from granules; after 2 h were 40,7% from microcapsules and 82,5% from granules, while the conventional tablets available on the market release 99,86% AC after 20 minutes.

CONCLUSIONS: We have reached prolonged release of AC due to microcapsulation/granulation process using natural polymers. Microcapsulation prolonged the release considerably more. Our future efforts will lead to the study of mucoadhesive properties of mentioned polymers.

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P5/7

Bile acid microvesicules as pharmaceutical formulation for hydrophilic drug delivery

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INTRODUCTION: There is a number of drugs which oral bioavailability is increased when encapsulated into microvesicules. That could be due to accumulation at brush-border membrane of enterocytes, intestinal uptake of micron size particles through paracellular passage, endocytosis by enterocytes, and absorption via gut associated lymphoid tissue. Bile acids and their derivates can increase the bioavailability of different drugs like insulin, calcitonin, gliclazide, and cefiprom. Bile acids can also increase cefotaxime permeability through mucosa by the formation of micelles.

MATERIALS AND METHODS: Hydrophilic peptide-like drug cefotaxime was used as a model drug. It was studied the influence of microvesicules formation with bile acids 3alpha,7alpha-dihydroxy-12-keto-5beta cholanate (MKC) on cefotaxime pharmacokinetics. Microvesicules loaded with cefotaxime with and without MKC were prepared by the rotary film evaporation method. Wistar laboratory rats were dosed orally with 15 mg/kg cefotaxime. Cefotaxime was dosed in the form of solution without or with MKC (2 mg/kg) or in the form of microvesicules without or with MKC. Blood samples were taken into the heparinised tubes from the tail vein. Plasma was separated and analysed by HPLC method [1]. Pharmacokinetics parameters were calculated by WinNonLin software.

RESULTS: After the oral administration of cefotaxime solution with MKC Cmax and AUC were 2-fold higher than after administration cefotaxime solution alone. After the administration of cefotaxime encapsulated in microvesicules with MKC, Cmax was 12- and AUC was 9-fold higher than administration of cefotaxime solution alone. After the administration of cefotaxime encapsulated in microvesicules without MKC, Cmax was 1,5 and AUC 2-fold higher than after administration cefotaxime solution alone. Pharmaceutical formulation of cefotaxime in the form of mikrovesicules with MKC had higher oral bioavailability in comparison to cefotaxime solution and cefotaxime encapsulated in mikrovesicules without MKC.

CONCLUSION: Bile acids microvesicules could be useful pharmaceutical formulation for the enhancement of hydrophilic peptidomimetic drugs oral absorption.

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P5/8

The influence of sodium dodecyl sulfate on diclofenac sodium and paracetamol release from hydroxypropyl methylcellulose tablets

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INTRODUCTION: Interactions between sodium dodecyl sulfate (SDS) and hydroxypropyl methylcellulose (HPMC) are described in the literature [1].

The aim of this study was to assess the influence of SDS on dissolution of diclofenac sodium (DF-Na) or paracetamol (PCM) from HPMC matrix tablets. Due to different solubility of model drugs different influence of SDS is expected; and the impact of possible SDS-HPMC interactions, which were also monitored in experiments, is additionally anticipated.

MATERIALS AND METHODS: 400 mg tablets, comprising 75% HPMC (Metolose 90SH 4000SR), 25% DF-Na or PCM and 0.5% of magnesium stearate were prepared by direct compression. Dissolution studies were carried out in USP II paddle apparatus (Agilent 708-DS, Agilent Technologies, USA) at 37 ± 0.5 °C and 75 rpm. As dissolution media, 900 mL of 4-times diluted McIlvaine buffer pH 4 without or with SDS of different concentrations (0.05–2% (w/v)) were used. Turbidity determination was used for SDS-HPMC interaction evaluation. Dispersions with different combinations of HPMC (0.3–1 g/L) and SDS (0.01–0.5%) were prepared and their transmittance was measured at 500 and 800 nm.

RESULTS: Drug release increases with increasing concentration of SDS for both, DF-Na and PCM with the exception of media with 0.05% SDS. However, PCM tablets are much less affected by increasing concentration of SDS than tablets with DF-Na. These differences can be attributed to different solubility of tested drugs at selected media pH value. Namely, SDS has higher solubilisation effectiveness if the solubility of drug is lower. Transmittance of HPMC and SDS dispersions is considerably lower at SDS concentrations close to 0.05% for all tested combinations with HPMC. The observed turbidity is probably a consequence of SDS-HPMC interactions which might be reflected also in dissolution profiles in the same SDS concentration range.

CONCLUSION: The influence of SDS on dissolution was more expressed in the case of drug with lower solubility. According to turbidity measurements of HPMC and SDS dispersions, SDS-HPMC interactions might have an additional influence on model drugs dissolution performance.

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P5/9

An investigation into drug release from high drug loaded granules prepared with poly(ethylene) oxide and carbomer

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INTRODUCTION: Multiparticulate drug-delivery systems represent flexible platform for modified drug release providing reduced risk of dose-dumping, inter- and intraindividual variations. High drug loading formulations are generally preferred, however reproducible drug release remains a challenge, especially in the case of highly soluble drugs [1, 2]. The aim of this study was preparation of sustained release granules with high caffeine load and low concentration of poly(ethylene) oxide or carbomer as swellable polymers.

MATERIALS AND METHODS: Granules containing 80 or 90% caffeine and 5 or 10% poly(ethylene) oxide (PEO, Polyox WSR303) or carbomer (Carbopol 971P) were prepared by kneading with water or ethanol as granulation liquid, respectively. Microcrystalline cellulose (MCC) was added as filler, where applicable. Swelling index of the investigated samples was determined based on the volume increase after 24h-exposure to aqueous media. Drug release testing was performed in the rotating basket apparatus at 75 rpm, in water as medium.

RESULTS: The granules exhibited notable differences regarding swelling properties, which were more prominent in carbomer samples. The

highest swelling index (10-fold volume increase) was observed for the sample containing 80% caffeine, 10% carbomer and 10% MCC (C2), while granules containing 90% caffeine and 10% carbomer (C4) swelled the least. Samples prepared with PEO exhibited modest swelling index which was not notably affected by the composition. Similarly to carbomer granules, the lowest swelling index was observed for the sample containing 90% caffeine and 10% PEO (P4). Addition of MCC contributed to sample processability.

All the investigated samples exhibited sustained drug release with the amount of caffeine released after 8 hours ranging from 35% (sample C2: 80% caffeine, 10% carbomer) to 85% (samples with 5% PEO). Carbomer granules exhibited zero-order drug release kinetics, which corresponds to their high swelling index.

CONCLUSIONS: High drug-loaded, sustained release granules have been prepared with relatively low polymer concentration. Samples containing carbomer exhibited higher swelling index and zero-order drug release kinetics.

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P5/10

The Effect of Ball Milling and Spray Drying on Phase Transition, Particle Size Reduction and Dissolution of Bicalutamide

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INTRODUCTION: The increase in apparent solubility of amorphous active pharmaceutical ingredients is an advantage [1], however the inherent stability stays as a major limitation and thus the formation of solid dispersions with polymers having high glass transition temperatures has been introduced.

The work presented herein is aimed at amorphization of bicalutamide upon either high energy ball milling or spray drying with Kollidon®VA64 and determination of the interplay between phase transition, particle size reduction and dissolution of the drug in solid dispersions and tablets.

MATERIALS AND METHODS: Bicalutamide (BCL, Hangzhou Hyper Chemicals Limited, China) was processed with Kollidon® VA64 (BASF, Germany). Sodium lauryl sulfate (SLS, BASF, Germany) was used to prepare dissolution medium. The samples were prepared using planetary ball mill Pulverisette 7 (Fritsch, Germany) and Büchi Mini Spray Dryer B-191 (Switzerland). Molecular structure of solid dispersions were tested by the use of Mettler–Toledo DSC1 STARe System (Switzerland), X-ray diffractometer Rigaku Mini Flex II (Japan) and the Nicolet iS10 FT-IR spectrometer (Thermo Fisher Scientific, USA). Particle size was determined using Phenom Pro desktop electron microscope (Nederlands) and Mastersizer 3000 (Malvern, UK), while the dissolution was analyzed in the pharmacopeial paddle dissolution apparatus Vision Elite8 (Hanson Research, USA) equipped with VisionG2 AutoPlus Autosampler. Solid dispersions were compressed using a single punch tableting machine (Korch EK0, Germany).

RESULTS: The results show that both applied processes led to amorphization of bicalutamide which is sufficiently stabilized by Kollidon® VA64. The effect of tableting on molecular structure of solid dispersions was assessed.

Particle size and morphology were affected by the applied processes. Particle size reduction were more significant for the spray-dried samples as they exhibited smaller particles with narrower distribution.

The dissolution profiles of BCL varied depending on the composition of the binary system, however ca. 10-fold enhancement was obtained in comparison to pure drug.

CONCLUSION: Co-milling and spray drying of bicalutamide with Kollidon® VA64 led to amorphization and significant improvement of the drug dissolution.

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P5/11

Investigation of formulation variables influencing the drug release rate from immediate release lamotrigine tablets by experimental design

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INTRODUCTION: Since lamotrigine has a good permeability and low solubility, the formulation composition is very important for the release of the active principle. Interactions between lamotrigine and excipients can cause fluctuations in blood concentration of lamotrigine, which may lead to adverse effects [1]. The objective of this study was to evaluate the effects of excipients (filler, disintegrant and lubricant) and storage humidity conditions on physical characteristics and dissolution rates of lamotrigine immediate release tablets.

MATERIALS AND METHODS: A 2^3 full factorial design (3 factors on 2 levels) was used in analyzing the effects of formulation composition (lactose or microcrystalline cellulose used as fillers, magnesium stearate as lubricant, sodium starch glycolate as disintegrant). Formulations were tested according to the 9th European Pharmacopoeia. In vitro dissolution test was performed in two media pH 1.2 and pH 6.8 (USP40), content analysis was carried out by UV/VIS spectrophotometry at 267 and 304 nm [2]. ANOVA test was used for results comparison.

RESULTS: Tablet formulations with microcrystalline cellulose (MCC) exerted better compressibility, friability and disintegration. Lactose formulations, in both media, released more than 85% of lamotrigine in the first 15 minutes, except T3 (high disintegrant, low lubricant content). MCC formulations showed lower release of lamotrigine, as only T8 (high lubricant and high disintegrant content) released more than 85% of lamotrigine in the first 15 minutes, in both media. In reduced (30%) and elevated (75%) humidity conditions, MCC tablets showed reduced dissolution rate of lamotrigine, while no significant changes were observed for lactose tablets.

CONCLUSION: Low concentrations of magnesium stearate and sodium starch glycolate led to slightly higher dissolution rate of lamotrigine, lower strength, friability and disintegration for lactose tablets. However, for MCC tablets this led to higher dissolution rates and strengths and had no significant effect on friability and disintegration. The obtained results demonstrate the importance of understanding interactions of excipients and active substances.

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P5/12

Influence of the storage humidity conditions on dissolution profiles of brand and generic lamotrigine immediate release tablet formulations

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INTRODUCTION: Lamotrigine is an antiepileptic drug, placed in group II of the Biopharmaceutical Classification System. The composition of the tablet formulation can significantly affect dissolution profile of the active substance. Although lamotrigine was shown to be stable under heat, humidity, and daylight stress factors, storage conditions may alter the dissolution profiles of lamotrigine tablets indirectly, through their impact on excipients [1]. We aimed to compare the dissolution profiles of brand and generic lamotrigine tablet formulations, as well as the influence of elevated and reduced moisture content at room temperature on the tablet characteristics and dissolution profiles of lamotrigine.

MATERIALS AND METHODS: Four formulations were tested before exposure to conditions of elevated (75±5%) and reduced (30±5%) moisture, as well as one and four weeks after exposure to these conditions. Tablet characteristics and lamotrigine dissolution rates were tested according to the requirements of European Pharmacopoeia

(Ph. Eur. 9) and American Pharmacopoeia (USP40). The dissolution profiles were tested in a medium of pH 1.2 and pH 6.8, and the content of lamotrigine was determined spectrophotometrically. Dissolution profiles were compared using model-independent and statistical method.

RESULTS: Formulation D in all tested conditions exerted different dissolution profile in comparison to formulations A, B and C. The effect of 75% moisture on lamotrigine release was more pronounced than the effect of 30% moisture. Under conditions of elevated moisture, the formulation D in the medium pH 6.8 released only slightly more than half of the declared content, and in other formulations less than 85% of the content was released in the first 15 minutes.

CONCLUSION: Exposure of tablets to the elevated moisture conditions may affect the tablet characteristics and the dissolution profile of lamotrigine. Therefore, keeping tablets out of the original package should be handled with caution, as it may potentially affect the therapeutic efficacy of lamotrigine tablets.

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P5/13

The choice of vehicle appropriate for co-administration of paediatric sprinkle pellets formulation with diazepam

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INTRODUCTION: During new medicinal products development appropriateness and acceptability in children must be considered. Several clinical trials showed very good acceptability of sprinkle formulations (pellets, minitablets) in paediatrics [1]. This dosage form in most cases requires co-administration with vehicles, like soft foods, to improve swallowability. However, food could influence the bioavailability of active substance [2]. In this study pellets with diazepam were formulated and in vitro disintegration and dissolution tests for pellets dispersed in water soluble gels were conducted to show any possible influence on performance of the primary drug formulation.

MATERIALS AND METHODS: Pellets with diazepam were prepared by extrusion and spheronisation technique (Caleva, UK) from mixture containing 0.5% of active ingredient, lactose and microcrystalline cellulose, wetted with water in a high shear mixer. Disintegration test was performed using a texture analyser disintegration rig (Stable Micro Systems, UK). Dissolution test was carried out in basket apparatus (100 rpm) with 500 ml of 0.1M HCl as dissolution medium (Pharma Test, Germany). Pellets (1 g containing 5 mg of diazepam) were placed in the basket, either loose or dispersed in 0.5% Carbopol 974P (PAA) or 2% high viscosity carmellose sodium (CMC) gels.

RESULTS: In the first step spheronisation process was optimised and the best particle size distribution and sphericity were obtained for 30 g batches spheronised for 8 min with 1500 rpm bowl rotation speed. Particles 1-1.25 mm were chosen for further studies. Diazepam pellets were characterised by disintegration time within 3 min in water and 4 min in 1% CMC gel. Dissolution tests showed similar dissolution rate (80%of the dose dissolved in 10 min) for loose pellets and dispersed in PAA, due to carbomer viscosity decreasing in acidic pH. Whereas, pellets dispersed in CMC gel exhibited very slow release of diazepam (only 10% was dissolved during 0.5 hour dissolution test).

CONCLUSIONS: The study showed that high viscosity water soluble gels like carmellose sodium used to facilitate drug administration could delay drug dissolution in acidic pH (stomach). While polyacrylic acid could be an excellent vehicle for sprinkles because of strong reduction of viscosity in acidic pH.

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P5/14

An investigation into the influence of preparation method and carrier type on the characteristics of liquisolid systems

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INTRODUCTION: Liquisolid systems (LSS) are dry-looking, powdered forms of liquid drugs or drug solutions/suspensions [1]. Liquisolid admixtures can be used for tablet production, but both good flowability and good compression properties have to be achieved. The published results dealing with the compression of liquisolid mixtures and preparation of LSS by using equipment commonly applied in pharmaceutical industry are still very scarce [2, 3]. The aim of this study was to investigate the flowability, resistance to crushing and wetting properties of LSS prepared by using three different carriers. The suitability of fluid bed processor as the equipment for preparation of LSS was also evaluated.

MATERIALS AND METHODS: Microcrystalline cellulose (MCC), Neusilin® US2 and Fujicalin® (Fuji Chemical Industry Co, Ltd, Japan) were used as carriers, colloidal silicon dioxide as a coating agent, and polyethylene glycol 400 as a liquid phase. Liquid content in LSS prepared corresponded to the optimum load factor (Lo) determined for each carrier. Liquisolid admixtures were prepared in Mycrolab fluid bed processor (OYSTAR Hüttlin, Germany) and compressed on eccentric tablet machine EKO Korsch (Korsch AG, Germany).

RESULTS: LSS prepared in fluid bed processor showed both better flowability and better mechanical properties than those prepared by using mortar and pestle. Considerably better flow properties were observed when Neusilin® US2 and Fujicalin® were used as carriers. Liquisolid compacts with Neusilin® US2 showed the best mechanical properties, despite having the highest liquid content (Lo values for Neusilin®, Fujicalin® and MCC were 1.09, 0.3 and 0.2, respectively). The lowest wetting time was observed in the case of compacts prepared with Fujicalin®. Higher degree of water uptake was observed at lower liquid loads, irrespective of the carrier used.

CONCLUSION: The results of the present study indicate that Neusilin® US2 can be used as a carrier in liquisolid tablets with high liquid content. Fluid bed processor was found to be suitable equipment for production of LSS.

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P6- DERMAL AND TRANSDERMAL DELIVERY 2.

P6/1

Rheological characterization of topical emulsion systems co-stabilized with an exopolysaccharide – A levan case study

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INTRODUCTION: Recent studies favour the increase of drug delivery systems' biocompatibility [1]. However, the selection of natural-origin excipients suitable for dermal application is somewhat limited, mainly due to their poor sensorial properties. Microbial levan is a water soluble complex fructan attributed with a broad spectrum of potential applications (e.g. co-stabilizer, film-former, antioxidant, cross-linker, plasma expander, etc.) [2]. This study is focused on levan's contribution to rheological properties of topical emulsion systems stabilized with either synthetic or natural-origin mixed emulsifiers.

MATERIALS AND METHODS: The addition of levan obtained from Bacillus licheniformis NS032 strain was varied (0, 0.2, 1 or 3%, w/w) in creams stabilized with: 1) a synthetic/anionic mixed emulsifier (Cetostearyl Alcohol (Type A), Emulsifying – comprising Cetostearyl Alcohol & Sodium Cetostearyl Sulfate), and 2) natural/non-ionic mixed emulsifier of the alkyl polyglucoside type SepineoTM SE 68 (Cetearyl Alcohol & Cetearyl Glucoside, Seppic, France). Rheometer Rheolab MC 120 (Paar Physica, Germany) was used for the evaluation of changes in colloidal structure and preliminary physical stability of both types of the investigated samples in a predetermined period of time (initially, after 1 and 3 months storage).

RESULTS: Levan proved to be a co-stabilizer compatible with both anionic and non-ionic emulsifiers, not compromising the initial shear-thinning flow behaviour with moderate to pro-

nounced thixotropy. Although levan is known for self-assembling in compact globules, these structures managed to retain sufficient flexibility and successfully complement both the matrix-type (in case of anionic mixed emulsifier) and lamellar liquid crystalline-type colloidal structure (generated by the non-ionic emulsifier). Apart from comparative analysis of the flow curves, fine time-dependant changes in hysteresis values successfully revealed a deeper impact of levan addition.

CONSLUSION: Increase in levan concentrations does not result in linear changes of key rheological parameters, which implies that even the lower amounts may successfully tailor pharmaceutical formulations.

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P6/2

Halloysite-functionalized chitosan films for local delivery of antibiotics

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INTRODUCTION: Polymeric films as drug carriers should exhibit biocompatibility, sufficient drug loading, flexibility, stability, target residence time, and adequate drug dissolution rate. These functional properties could be improved by the addition of minerals, such as clays [1]. Among them, halloysite nanotubes (HNTs) are particularly attractive, owing to their biocompatibility, specific nanotubular structure and excellent dispersibility in solutions of polymers. The objective of this work was to investigate the influence of HNTs on chitosan film properties relevant for local delivery of antibiotics.

MATERIALS AND METHODS: Chitosan and chitosan-HNTs composite films were prepared by casting and solvent evaporation technique. Briefly, required amount of HNTs was dispersed in 1.5% (w/w) chitosan (MW 253.7 ± 7.8 kDa; deacetylation degree >85%) and 0.5% (w/w) tetracycline hydrochloride (TH) solution (chitosan/HNTs ratio = 3/1). The dispersion was casted into acrylic molds and dried at room temperature. Obtained films were cut into 25 x 25 mm pieces, subjected to mass and thickness determination, FT-IR, mechanical, and thermal analysis, and in vitro drug release studies. For comparison, chitosan films were prepared by following the same procedure without addition of HNTs.

RESULTS AND DISCUSSION: TH-loaded composite films were 89.12 ± 6.83 μm thick while their mass was 76.70 ± 3.29 mg. The addition of HNTs caused decrease of elongation at break from 60.94 ± 5.05 % to 21.65 ± 2.65 % and increase of mechanical resistance, that was tensile strength from 24.66 ± 2.56 MPa to 134.8 ± 13.21 MPa and elastic modulus from 40.45 ± 2.16 MPa to 633.79 ± 128.37 MPa, as a result of interactions between HNTs and chitosan confirmed by FT-IR analysis. DTA and TG studies revealed increased thermal stability of the composite films in comparison to the chitosan films. The composite films exhibited more sustained release than chitosan films, with t50% < 5,5 h (t90% > 8 h) and t50% < 2 h (t90% > 8 h) in phosphate buffers 5.8 and 7.4, respectively. The observed influence of pH on TH release from the composite films could be ascribed to pH-sensitive interaction between HNTs and chitosan.

CONSLUSION: Halloysite-functionalized chitosan films demonstrated better potential for local delivery of antibiotics in comparison to chitosan films owing to the improved thermal stability, mechanical and drug-release properties.

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P6/3

Investigation of DPPH radical scavenging ability of different antioxidants incorporated into fast inverted oil-in-water emulsion

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INTRODUCTION: The SWOP (SWitch-Oil-Phase) emulsions are oil-in-water emulsions which are characterized by fast inversion into water-in-oil emulsions during application on the skin and consequent formation of a water-resistance layer over the skin [1]. Flavonoids quercetin (QUE) and dihydroquercetin (DHQ), as well as β-carotene (βC) are used in cosmetics as antioxidants. Additionally, these compounds show protective effects against ultraviolet radiation. Therefore, their incorporation into SWOP emulsion could result in a new waterproof sun protection product. The aim of this study was to prepare SWOP emulsion with 0.5% QUE (SQUE), 0.5% DHQ (SDHQ) and with combination of 0.5% DHQ and 0.2% βC (SDHQβC), and to evaluate DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging ability of incorporated antioxidants in comparison to the pure compounds.

MATERIALS AND METHODS: For this purpose, in vitro colorimetric DPPH assay was used [2, 3]. Results were expressed as the concentrations of antioxidants that scavenged 50% DPPH radicals, and analysed by one-way ANOVA, followed by Tukey's post hoc test (p=0.05).

RESULTS: QUE and DHQ incorporated into SWOP emulsion exhibited strong anti-DPPH activity, without significant statistical difference compared to the pure compounds. The SC50 values of incorporated and pure QUE were 3.48±0.10 and 3.37±0.03 μg/mL, respectively. The SC50 values of DHQ incorporated in SDHQ and SDHQβC, and of pure DHQ were 5.36±0.27, 5.06±0.14 and 5.02±0.10 μg/mL, respectively. Neither incorporated nor pure βC showed anti-DPPH activity at tested concentrations (0.40-8.00 μg/mL). The SC50 values of tested SWOP emulsions, i.e. SQUE, SDHQ and SDHQßC were 0.70±0.02, 1.07±0.05, 1.01±0.03 mg/mL, respectively.

CONCLUSION: QUE and DHQ incorporated into SWOP emulsion retain their strong anti-DPPH activity, i.e. investigated SWOP emulsion is a suitable vehicle/base for the tested flavonoids. On the other hand, although known for its antioxidant activity, βC showed no anti-DPPH activity, which is in agreement with findings of some other authors [4]. Therefore, DPPH assay is not suitable for the testing of antioxidant activity of βC incorporated into SWOP emulsion.

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P6/4

Adapalene loaded alkyl polyglucoside based topical microemulsions – in vitro drug release

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INTRODUCTION: In order to enhance dermal availability of the anti-acne drug adapalene (ADA) into target areas, microemulsion (ME) formulation appeared to be a promising tool [1]. The aim of this study was to evaluate the composition influence of previously formulated MEs [2, 3] based on naturally occurring nonionic surfactants - alkyl polyglucosides, on in vitro release of ADA.

MATERIALS AND METHODS: For the preparation of MEs, oil (propylene glycol monocaprylate, glycerol monocaprylate or glycerol monocaprylocaprate) was added to the mixture of surfactant (decyl glucoside or caprylyl/capryl glucoside) and cosurfactant (propylene glycol) and mixed for 15 min. Then, proper amount of water was added and mixed for another 15 min. ADA (0.1% w/w) was dissolved in previously prepared MEs. pH, conductivity and viscosity of all MEs were measured. The microstructure of the selected vehicles was assessed by using electrical conductivity measurements and differential scanning calorimetry in cooling mode. In vitro drug release studies were conducted using Franz Diffusion cells.

RESULTS: All MEs were transparent, low-viscous (26.81-42.18 mPa*s) colorless liquids. In order to be dermatologically acceptable, measured pH values (above 8) had to be adjusted. According to the electrical conductivity and DSC measurements, bicontinuous microstructure was assigned to each ME. In vitro drug release profiles exhibited slow release rates during the first 1-2 hours and the last 4 hours. The type of surfactant seemed to play an important role, since ADA release from ME based on caprylyl/capryl glucoside was lower than from the sample based on decyl glucoside.

Monoglycerides significantly increased the amount of the drug released, although the influence of glycerol monocaprylocaprate, having slightly longer alkyl chain length than glycerol monocaprylate, was more pronounced.

CONCLUSIONS: Since ADA release from bicontinuous MEs was sustained, drug retention within the skin for prolonged period and a reduction of drug concentration dependent irritation could be expected. However, the selected formulations need to be subjected to further permeation and penetration studies.

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P6/5

Towards a deeper insight into levan's skin hydration effect

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INTRODUCTION: Although every review on levan suggests its hydratig potential there is a lack in published data dealing with this issue [1]. Therefore, we were interested to investigate levan's hydrating efficacy, when incorporated in different vehicles, with the use of in vivo and in vitro methods.

MATERIALS AND METHODS: Different vehicles, of gel and emulsion type were prepared. Cream samples contained 0% (placebo), 0.5% or 1% (w/w) of levan. As for gels, beside placebo and samples with levan, two more samples- one with 10% (w/w) of glycerol and one with 10% (w/w) of glycerol and 1% (w/w) of levan were prepared. Performed in vitro occlusion test used the glass beakers, purified water and a sample-covered filter paper (32±0.5°C for 48h). The occlusion factor was calculated after 4, 24, and 48h. Additional test, performed only with creams, used the pig ear skin and Franz cells with similar procedure. In vivo efficacy study was conducted as 6- and 24-h study (Corneometer®CM825, Courage&Khazaka-Germany).

RESULTS: Occlusion investigation indicates that the addition of levan contributes to the occlusion effect of gels and emulsions. On the other side, samples with levan induce a decrease in stratum corneum hydration, compared to initial values and placebo samples, and this decrease is more pronounced within gels. Although not significant, the decrease is evident after 1 and 4h, while after 6h the results went back to initial values. For emulsions, 24-hour study showed that the addition of levan enabled a prolonged hydration effect.

CONCLUSIONS: All obtained results indicate that levan is able to attract and bond water, thus acting more like a film-forming rather than hydrating agent, especially within gels. Levan shows different effects depending on the vehicle used. Its ability to bond water and to make a film on the skin surface in investigated emulsions contributes to the prolonged hydrating effect. Finally, results indicate that levan could be used as an excipient which enables prolonged and/or modified delivery of actives.

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P6/6

Investigation of the effect of zinc oxide on the barrier function on baby skin

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INTRODUCTION: The structure and function of baby skin is significantly different from the skin of adults. The infant skin is made up of three layers, but each layer is thinner and more vulnerable. The skin of infants and children is extremely exposed to the harmful effects of the environment: pathogenic microorganisms, thermal and mechanical effects and chemical agents. The barrier function can be improved with a proper emollient

treatment, so it is an important target to develop preparations which support the barrier function of baby skin.

The parameters of skin physiology undergo dynamic changes during the first 3 months of life, especially during the neonatal period. These rapid changes during the first months after birth are reflected in measurements of biophysical parameters, such as TEWL and skin-surface pH, as well as measures of the total water content of the SC, water gradient through the SC and water absorption and desorption rates in the skin.

The aim of this work was the formulation and investigation of a science-based semi-solid formulation with zinc oxide content that is readily available in everyday pharmacy practice and which may support the barrier function of baby skin.

MATERIALS AND METHODS: In our research work we investigated the moisturizing effect and the transepidermal water loss (TEWL) of the developed formulation with Corneometer and Tewameter. Furthermore, we measured the in vitro UVB Protection Factor (Sun Protection Factor/ SPF) of the preparations. Zinc oxide as a topically used excipient acts as a protective coating in case of mild skin irritations and abrasions. It can promote the healing of chapped skin and diaper rash. Zinc oxide works as a mild astringent, sun protection agent and has some antiseptic properties.

RESULT AND CONCLUSION: On the basis of our results, the zinc oxide containing cream increased the skin hydration in the short term but could not provide a long-lasting moisturizing effect. The application of zinc oxide in the used concentrations decreased the transepidermal water loss significantly. Furthermore, based on transmittance results, increasing zinc oxide concentration increases the protection against UV radiation. However, 25% zinc oxide provides SPF 7 which is not enough to a perfect skin protection.

P6/7

Topical biocompatible fluconazole-loaded microemulsion-gels based on essential oils and sucrose esters: formulation, evaluation and in vitro skin permeation of drug

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INTRODUCTION: Among various vehicles investigated in the last decades for fluconazole (FZ) topical delivery, microemulsions (MEs) and microemulsion-gels (MEGs) have attracted great interest due to their thermodynamic stability and high capacity to solubilize the drug and to increase its penetration through the skin. Selecting biocompatible excipients in their formulation, make MEs/ MEGs prospective non-toxic and non-irritating vehicles for safe topical drug delivery. This study aims to develop topical innovative FZ-loaded MEs based on natural, biodegradable and biocompatible excipients, namely essential oils (EO), sucrose esters (sucrose laurate, SL or sucrose palmitate, SP) and chitosan. EO were selected also for their reported antifungal activity in order to enhance fluconazole's therapeutic effect.

MATERIALS AND METHODS: FZ as active ingredient, three EO (clove oil, oregano oil or cinnamon oil) mixed with isopropyl myristate (1:1) as oil phase, SL or SP as non-ionic surfactants, isopropyl alcohol as cosurfactant, chitosan as gelling agent and 2% acetic acid solution as aqueous phase were used to prepare ten MEG formulations. The FZ solubility in two synthetic oils (isopropyl myristate and ethyl oleate) and nine EO with intrinsic antifungal activity (eucalyptus, lemongrass, clove, cinnamon, peppermint, lavender, sweet fennel and oregano oil) were studied. The selection of the oil phase and cosurfactant were based on their maximum solubilizing capacity of the drug and surfactant respectively. Pseudoternary phase diagrams were constructed using the micro plate dilution method in order to identify the ME existence domains, from which ten ME formulations were selected. The influence of the formulation variables (type and percentage of EO and sucrose ester) on the physicochemical and rheological MEGs properties and on the in vitro FZ permeation through pig ear skin were studied.

RESULTS: The results of in vitro FZ skin permeation and antifungal activity studies confirmed the superiority of two MEG formulations based on cinnamon EO and SP or SL, and also a MEG formulation based on oregano essential oil and SP;

these MEGs conducted to the highest values of the flux and inhibition zone diameter.

CONCLUSION: The studied biocompatible MEGs based on EO and SP or SL and gellified with chitosan proved to be versatiles carriers for simultaneous topical delivery of two bioactive components (FZ and EO).

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P6/8

Influence of cholesterol oleogels on the in vitro release of poorly soluble drug

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INTRODUCTION: Oleogels are defined as the semi-solid systems, in which an organic liquid phase is immobilized by a three-dimensional network composed of gelator fibers [1]. Their preparation and use have recently generated a great interest for scientific and technological reasons [1, 2].

This work evaluates the influence of oleogels composed from cholesterol as oleogelator and two different liquid phases – castor oil and liquid paraffin on the release of poorly soluble drug - allylamine antimycotic Terbinafine hydrochloride.

MATERIALS AND METHODS: Oleogels were prepared by dispersion of cholesterol in castor oil or liquid paraffin at 60°C and cooled to room temperature under continuous stirring. Prepared oleogels were characterized in terms of their rheological properties using rotary viscometer.

Because of the limited solubility, terbinafine (0.5% w/w) was solubilized in O/W microemulsion and subsequently dispersed in oleogels in the ratio 1:4.

Influence of formulation on the release was determined using Franz diffusion cells through the cellulose membrane. The amount of permeated drug was analyzed spectrophotometrically at 224 nm.

RESULTS: The permeation profile indicates some correlation between the rheological properties and the drug release. Oleogels with liquid paraffin had lower viscosity compared to oleogels with castor oil. The drug release data also show that the highest amount of terbinafine was released from oleogels of cholesterol in liquid paraffin. The results indicate that the lower viscosity can lead to better drug motility which improves drug flux across the membrane [3].

CONCLUSION: The release of the drug depended on its diffusion according Higuchi kinetic model (R^2 = 0.9871). The highest cumulative amount of Terbinafine hydrochloride (45.13 μg/cm^2) was released from the formulation of cholesterol (3% w/w) and liquid paraffin.

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P6/9

The influence of chiral enhancers on stereoselectivity in transdermal permeation of flurbiprofen

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INTRODUCTION: Enantiomers of chiral drugs might often differ in their pharmacological, toxicological and pharmacokinetic properties [1]. Considering that skin is naturally chiral enviroment of optical active molecules of ceramides in stratum corneum, the different permeation of chiral compounds is possible to expect. Any stereoelctivity in transdermal absorption would affect the pharmacological activty of racemate. The Racemic flurbiprofen, is effective nonsteroidal anti-inflammatory agent and exhibits stereoselctivity in action and disposition [2]. Topically applied flurbiprofen is used for treatment of gingival inflammation and soft tissue rheumatism [3]. Our preliminary studies confirmed stereoselectivity in transdermal permation of single enantiomers of flurbiprofen through rat skin [4]. The object of our work was the evaluation of influence of stereochemistry of chiral alcohol enhancer on the transport of racemic (RS)-flurbiprofen and its single enantiomers.

MATERIALS AND METHODS: The permeation study was performed through porcine skin by using Franz diffusion cells. The donor vehicle consisting of flurbiprofen in PBS and of alcohol chiral enhancers (from butan-2-ol to decan-2-ol). The acceptor phase containing PBS buffer. The enantiomers of flurbiprofen were determined using stereoselective HPLC method.

RESULTS: The influence of alcohols chirality on the permeation of flurbiprofen enatiomers was tested. In presence of different alcohol enhancers the permeation profiles of the enantiomers of flurbiprofen from its racemic form were comparable When donor solution contained pure enantiomers, the marked differences were observed between the permeation rates o (R)-flurbiprofen and (S)-flurbiprofen. The most effective for skin permeation were combination to the same stereochemistry of drug enhancer: (R)-flurbiprofen with (R)-alcohols and (S)-flurbiprofen with (S)-alcohols. The highest enhancing effect was detected for (R)-hexanol.

CONCLUSION: The influence of chiral alcohols on different permation of flurbiprofen enantiomers was observed in permeation of its single enantiomers. The significant difference in permeation of enantiomers from racemic flurbiprofen was not proved.

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P6/10

Mechanism of in vitro release kinetic of meloxicam, tenoxicam and indomethacin from hypromellose matrices

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INTRODUCTION: In our previous work, three NSAIDs (meloxicam, tenoxicam and indomethacin) were individually included in four types of polymeric matrices (PM 1-4), based on hypromellose, as part of new formulations development process [1]. Three of them (PM 1-3) were further subjected to the release/permeation test by the Franz method, determining the in vitro release profiles. This study aims to analyze their release kinetics mechanism.

MATERIALS AND METHODS: The release profiles grouped by the type of matrix and expressed as mean of each point of profiles were fitted in DDSolver, over the period of time at which no more than 60% of the NSAID dose was released, using the Korsmeyer Peppas (KP) function in three variants: KP (model M1), KP with Tlag (M2), and KP with F0 (M3); and Akaike index (AIC) as goodness of fit parameter [2]. Statistical analyzes were performed in GraphPad Prism.

RESULTS: The NSAIDs release kinetic was found as being based on non-Fickian processes (nKP < 0.89). In all cases, the diffusion of NSAID in the matrix mass depends both on the hydration and relaxation of the polymer [3]. Analysis of variation between data groups (two-way Anova, alpha = 0.05) showed that the type of matrix insignificantly influences the mechanism of releasing. M2 fits the best all of the analysed profiles, AIC having in all cases the smallest values (18.2 - PM1, 18.3 - PM2, 6.94 - PM3). The constant of the release process (kKP-Tag) decreases in the order of PM2 < PM1 < PM3.

CONCLUSION: The three studied types of hypromellose matrix release in vitro the NSAIDs by the same type of kinetics. The calculated parameters will be used further in formulation optimization studies.

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P6/11

The influence of propylene glycol concentration as a modulator of the indomethacin permeation from dermal films

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INTRODUCTION: Indomethacin is an active substance which administered orally is bioavailable and absorbable in the blood flow even if its water solubility is extremely low (0.937 μg/mL). Indomethacin absorption is based on high permeability of the biological membrane for this type of molecule (Mr - IND: 357.79 g/mol), and it is favoured also by its lipophilic character (log P - IND: 0.91 at pH 7.4 and 4.27 at pH 2.0) [1, 2]. The most important barrier for the released substance from a transdermic therapeutic system (TTS) is the corneous layer which at its surface has an acid pH with a protection physiological role. The aim of the current study consisted in a comparative analysis of the effects on the permeability through the biological pig skin membrane at the pH of 5.5 and 7.4, and the evaluation of the influence of different concentrations of propylene glycol from the TTS.

MATERIALS AND METHODS: Indomethacin (Sigma Aldrich Milan, Italy); HPMC15000 (Shin-Etsu Chemical Co., Ltd. Tokyo, Japan); propylene glycol (Scharlau Chemie, Barcelona, Spain); ultrapure water (Millipore Direct-QSdistiller), ethanol (Chemical Company, Romania); Tween20 (Sigma Aldrich Co., France). Two formulations of dermal films based on 1.5 % of HPMC15000 and with a composition of 10 % (FI1) and 30 % (FI2) propylene glycol were prepared through evaporation technique of the solvent. For the determination of indomethacin permeation through the biological membrane, Franz Cell diffusion method was used: receptor medium: phosphate buffer pH 5.5 and 7.4.

RESULTS: The analysis of the indomethacin diffusion from the proposed formulations showed that at pH 5.5 a concentration of 30 % propylene glycol in FI2 favoured the permeation of drug 10 % higher than the FI1, but also influenced negatively the flow through the biological pig skin membrane. In comparison, the pH approaching to neutrality increased three times the quantity of permeated drug in FI1 and 20 times in FI2. It has been observed that at a pH of 7.4 a higher concentration of propylene glycol in FI2 increased 10 times the flow rate through the testing membrane compared with FI1.

CONCLUSION: Permeation of indomethacine through the biological membrane from the formulations is influenced by the pH of the acceptor medium and also by the propylene glycol concentration.

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P6/12

Evaluation of miconazole nitrate in vitro permeation from dermal systems through synthetic vs. biological membranes

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INTRODUCTION: The development of pharmaceutical dosage forms containing miconazole nitrate (MN) intended for external use can bring various benefits to patients who are resistant to classical antifungal forms [1], since this active substance accumulates in the skin, acting as a slow release product [2]. This study aims to evaluate the in vitro capacity of MN to permeate through two types of membranes (nylon - Ms vs. skin of pig ear - Mb) during its releasing from two matrices based on hydroxyethyl cellulose (HEC).

MATERIALS AND METHODS: Samples of 2.54 cm^2 containing 40 mg MN (Sigma Aldrich, Germany) in 8% (FI) and 11% (FII) polymeric matrices of HEC (Ashland, Germany) with 4.0% (FI) and 3.6% (FII) of polyethylene glycol - PEG 400 were prepared in form of films with thickness of 0.23 mm (FI) and 0.30 mm (FII), by casting and solvent evaporation technique. The in vitro permeation curves of MN ($mg \bullet cm^{-2}$ vs. h) were determined by Franz method (cell of 14 mL, phosphate buffer at pH 7.4 with 0.045% sodium lauryl sulphate, 32±0.5 °C), assessing the MN from acceptor sample (5 mL) at 273 nm (Spectrometer UVD 3200, Labomed Inc., USA). The results were statistical analysed using GraphPad Prism.

RESULTS: Area under the permeation curves (AUC) was calculated for the period of 1 h to 24 h and had the following values: 164.5 (FI-Ms), 152.7 (FII-Ms), 78.61 (FI-Mb) and 62.44 (FII-Mb); with AUC-FI vs. AUC-FII statistically significant differences only for Mb ($p = 0.0154$; unpaired t test, con-

fidence interval of 95%), case in which the variance was insignificant (Anova one way, Tukey's test). The rate of MN permeation ($mg \bullet cm^{-2} \bullet h^{-1}$), expressed by the slope of the regression line, was significantly lower through Mb (0.28 - FI, 0.22 - FII) than through Ms (0.43 – FI, 0.38 – FII), with latency time (h) only in the Mb case (1.2 - FI, 0.89 – FII).

CONCLUSION: Compared with the synthetic membrane, the biological membrane reduces to almost half the in vitro permeation of MN released from HEC matrices, the differences found between the two dermal analyzed systems being mainly determined by the thickness of the membrane and the PEG content, used in formulations both as plasticizer and as promoter of absorption.

ACKNOWLEDGMENTS: This work was supported by the University of Medicine and Pharmacy of Tîrgu Mures Research Grant no. 275/6/11.01.2017.

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P6/13

Application of nanotechnology in formulation of tioconazole and melaleuca alternifolia essential oil for onychomycosis topical treatment

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INTRODUCTION: The topical therapy of widespread onychomycosis is a long process (10-12 months) and has low cure rate [1]. The hard keratin act as a barrier to drug diffusion, and its hydrophilic structure also reduces the diffusion of high molecular weight and lipophilic drugs. In order to enhance the penetration of drugs we can use diffusion enhancers or an appropriate formulation. The azole derivatives have broad antifungal spectrum and it can show synergism with essential oils (EOs) [2]. Tioconazole and melaleuca alternifolia EO have been chosen for this research. They can be applied as simple solution of tioconazole in EO, as solution of both in organic solvent as diffusion enhancer or in a form of emulsion. Pickering emulsions (PEs) are stabilized with nanoparticles (NP) instead of surfactant, which are used to stabilize conventional emulsions. With appropriate choice of nanoparticles and prudent formulation a selective and sustained drug delivery system can be prepared.

Our aim was to formulate tioconazole and Melalecua alternifolia essential oil PEs, which are suitable for onychomycosis topical treatment and examine their diffusion properties in a nail model membrane.

MATERIALS AND METHODS: Silica NPs modified with ethyl groups were prepared by modified Stöber method, they have been characterized with DLS and TEM. We have determined solubility of tioconazole in Melaleuca alternifolia essential oil, and we have apply their mixture to perform formulation of PEs. We have tested the ratio of oil phase to silica NPs and their concentration on the resulting droplet size and stability of PEs, which were determined with DLS measurements. In vitro diffusion studies in Franz cells through model membranes have been performed with all formula (solution, conventional emulsion and PE). Dissolution studies have also been performed.

RESULTS AND CONCLUSION: The droplet size of emulsion has a correlation with the NPs to oil ratio, we are still working on the diffusion and dissolution tests and final results and conclusion will be shown at the conference.

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P6/14

Nystatin-Flucytosine Liposomes for Fungal Nail Infection Treatment

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INTRODUCTION: Onychomycosis is challenging to treat [1]. Flucytosine has wide antifungal activity, however resistance has limited its use as monotherapy, necessitating combination or novel drug delivery [2]. Nystatin-flucytosine combination was reported to be synergistic [3], but their

use is difficult due to different solubilities and lipophilic nature of nystatin. Liposomes are appropriate for drug combinations as they are capable of encapsulating both lipophilic and hydrophilic drugs [4]. Liposomal loaded anti-fungal film was reported to have superior activity, making liposomes a promising anti-fungal nail infection therapy [5].

MATERIALS AND METHODS: The effect of nystatin on liposomal integrity was studied. Liposomes of different Phospholipon 90G and 90H phospholipids, cholesterol and nystatin ratios were prepared by reverse phase method. The optimum nystatin containing formulation was used to prepare flucytosine encapsulated liposomes. Briefly, components dissolved in ether were then injected with a flucytosine water solution. The formed water in oil emulsion was sonicated, and instantly injected into buffer, forming water in oil in water double emulsion. After further sonication, ether was evaporated by a rotary evaporator resulting in a liposomal suspension. Liposomes were characterized in terms of encapsulation, size and zeta potential. Dissolution, permeation, stability and microbiology studies followed to allow optimum formulation identification.

RESULTS: Liposomes with different size and drug loads were produced and evaluated regarding diffusion properties in nail model membrane. Preliminary results showed a good control over the size of the liposomes, which influenced the diffusion properties in the model membrane.

CONSLUSION: Presently we are working on the experiments. Final results and conclusion will be presented at the conference.

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P6/15

Development and investigation of Papaverine hydrochloride containing nanostructured systems for the treatment of erectile dysfunction

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INTRODUCTION: Papaverine hydrochloride (PaHCl) is an old, well-known drug with spasmolytic activity but it has therapeutic effect in erectile dysfunction, too. As an intracavernous injection, it is not used in urologic clinics today because the side effects of the injection are pain, scarring or priapism [1]. Our purpose was to develop and test a topical semi-solid preparation containing PaHCl [2], which provides an alternative administration option, eliminating the undesirable side effects of the injection.

MATERIALS AND METHODS: Lyotropic liquid crystal (LLC) systems were formulated as a semi-solid preparation with different concentrations of PaHCl. The characterization of the LLC structure was performed by polarization microscopy using a Leica image analyser and rheological measurements. The drug diffusion and penetration tests were performed with in vitro synthetic membrane and an ex vivo human epidermis using Franz diffusion cell. The human skin was investigated by Raman microscope to visualize the API in different skin layers.

RESULTS: The results of diffusion and penetration showed reverse concentration dependency. The in vitro and ex vivo studies correlated with each other and the results of Raman microscopy. The LLC structure influenced the penetration results, the lower viscosity and lamellar structure increased the penetration through the skin.

CONCLUSION: Based on our results, a PaHCl containing topically used LLC formulation may be a suitable and effective alternative to the injectable formulation.

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P7- NANOPARTICLES 2.

P7/1

Human respiratory epithelial cell culture models for pharmaceutical technology applications

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INTRODUCTION: Pulmonary administration of drugs is increasingly investigated and used as a novel and alternative drug delivery pathway. Culture models of the respiratory system are not only important to study drug transport and absorption, but they are useful tools to better understand the pathomechanism of pulmonary diseases, like cystic fibrosis. To mimick the in vivo complexity of the bronchial and alveolar epithelium and the underlying blood vessels co-culture systems are needed. Another important aspect of these models is the reconstitution of the air-blood barrier of the respiratory system. The establishment of the air-liquid interface in culture inserts is difficult. Our research hypothesis was, that artificial sputum medium (ASM) containing mucin, would provide a physiological microenvironment on the top of respiratory epithelial cells and this would help to create a better air-liquid interface culture model. Our aim was to establish and characterizein vitro respiratory epithelial models using human alveolar and human bronchialepithelial cellsco-culturedwith human endothelial cellsin different conditions and to test them with a model pharmacon.

MATERIALS AND METHODS: For the respiratory co-culture model systemshuman A549 alveolar epithelial cells [1], human CFBE bronchial epithelial cells [2], and human endothelial cells were used. To optimize the culture systems ASM, liquid/liquid and air/liquid conditions, and various pH and NaHCO3 levels were tested. The barrier properties were characterizedbytransepithelial electrical resistance measurements and permeability studies for marker molecules and a model pharmacon. The morphological properties were analyzed by immunohistochemical staining for junctional proteins.

RESULTS: The presence of endothelial cells induced better barrier properties in respiratory epithelial cells, as reflected by the higher resistance and lower permeability values for paracellular marker molecules. The co-culture conditions also increased the tightness of interepithelial junctions visualized by immunostainings. We also found effects on the co-culture systems when we tested ASM, liquid/liquid and air/liquid conditions, and various pH and $NaHCO_3$ levels.

CONLUSION: We successfully established and characterized new in vitroco-culture models for respiratory epithelium for which we provided physiologically relevant conditions and microenvironment. Theseair-blood barrier models are suitable for permeability studies and could contribute to the development of new methods to increase drug penetration across barriers and to more efficiently treat diseases.

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P7/2

Melatonin loaded polyanhydride nanoparticles for oromucosal application

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INTRODUCTION: Melatonin (MEL), a circadian synchronizing hormone, could provide a valid therapeutic strategy for treatment of gingivitis and periodontitis due to its antioxidant, antiinflammatory, immunomodulatory and osteogenic actions [1]. To further enhance its therapeutic potential, MEL was loaded into PEGylated nanoparticulate (NP) delivery system based on poly(methyl vinyl ether-co-maleic acid) anhydride (PVM/MA). This water-insoluble, mucoadhesive, non-toxic, synthetic co-polymer is able to form NP by simple solvent displacement and could be easily functionalized with different ligands [2]. NPs densely coated with low molecular weight polyethylene glycol (PEG) are able to readily penetrate the mucus layer, thus overcoming its barrier properties and rapid NP clearance from the application site [3].

MATERIALS AND METHODS: PEGylated NPs were prepared by solvent displacement method [2] and functionalised with PEG 4000, 6000 and 10 000 at 1:0.15 PVM/MA to PEG ratio, while MEL loading was performed at 1:10 and 1:5 MEL to PVM/MA ratio. NPs were characterised in

terms of the particle size and zeta potential. The level of PEGylation was determined by HPLC, while MEL encapsulation efficiency was calculated after UV/VIS quantification of unloaded MEL. NPs in the solid state were prepared by freeze-drying using sucrose, trehalose and glycine at 1-5 % (w/v) as cryoprotectors.

RESULTS: Unloaded PEG coated NPs were monodisperse with an average size in the range of 195.8 (NPPEG 4000) up to 219.3 nm (NPPEG 10000) and negative zeta potential of -40 mV. Sucrose at 5% (w/v) concentration appeared as the best cryoprotector. The NPs production yield varied from 51.9 – 56.5%. The highest PEGylation level of 93.0% was obtained for PEG 6000 coated NPs after 1h of incubation. The highest encapsulation efficiency of MEL in such NPs of 11.45% was obtained at indole to PVM/MA ratio of 1:5, resulting in particles of 164.3 nm in size and negative zeta-potential of -37.7 mV.

CONCLUSION: MEL loaded PVM/MA NPs coated with PEG 6000 showed of acceptable size and surface characteristics for mucopenetration and can be considered as a potential novel oromucosal delivery system for gingivitis and periodontitis treatment.

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P7/3

Caco 2 cellular uptake of ligand modified PLGA-PEG-PLGA nanoparticles

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INTRODUCTION: Evaluation of the internalization behavior of nanoparticles is of crucial importance for their safety and efficacy. It can guide us through the experimental design of NPs with enhanced active targeting and low toxicity. Having the background, the aim of this study was to compare the internalization behavior of biodegradable, folate- and hyaluronan-decorated, as well as ligand-free, fluorescently labeled NPs, composed of high Mw triblock PLGA-PEG-PLGA copolymer.

MATERIALS AND METHODS: The preparation of NP and their fluorescent labeling were described elsewhere [1]. The binding of FA and HA to the PLGA-PEG-PLGA polymer was performed using EDC/NHS chemistry. Particle size, size distribution and zeta potential of the NPs were determined by DLS. CLSM was used to acquire images from Caco2 cells exposed to the nanoparticles after 4 and 24h of incubation. The cellular uptake in Caco2 cells was quantified by measuring fluorescence intensity on microplate reader after 4h and 24h of incubation at 4 and 37°C.

RESULTS: The average hydrodynamic diameter for NP, NP-FA, NP-HA was 110.13±0.81nm, 107.86±1.3nm and 121.45±2.05nm, respectively, with unimodal size distribution for all formulations (PDI<0.2). The zeta potential was negative for all formulations, ranging from -19.43±1.09mV for NP, -12.14±2.17mV for NP-FA and -28.1±1.13mV for NP-HA. LSM images revealed that all formulations were internalized by Caco-2 cells, and the quantitative analysis demonstrated that 28.6% of the NP-FA, 20.3% of NP-HA and 18.6% of the NP were internalized in the first 4h at 37°C. After 24h incubation time, the internalized fractions of NP-FA, NP-HA and NP were slightly increased to 32.6%, 23.1% and 25.4%. Further, negligible NPs internalization at 4°C for all the samples, most probably points to possible ATP dependence of the internalization process. In the scope of the same study we are also trying to understand the kinetic and extent of NPs internalization using different cancer cell lines, compare the results and improve knowledge for the design of more efficient cancer targeting nanomedicines.

CONCLUSION: Attachment of FA and HA to PLGA-PEG-PLGA polymer, didn't affect the physical characteristics of the produced nanoparticles and probably induced changes in their surface. The ligand decorated NPs demonstrated favorable internalization behavior in Caco2 cells, which probably was ATP dependent.

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P7/4

X-Ray irradiated MWCNTs as drug carriers: characterization and release kinetics

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INTRODUCTION: Multi-walled carbon nanotubes (MWCNTs) were previously produced (by an original procedure of reduction of Li molten salts on a graphite cathode), subsequently exposed to X-rays (140 kV X-ray tube in a dose 716 mGy/cm) and adequately characterized [1, 2]. In this study, the effect of irradiation on their physicochemical properties and drug release was evaluated, after loading with risperidone (Risp).

MATERIALS AND METHODS: Solution of Risp in DMSO/water was added to (non-) irradiated MWCNTs and the dispersions were stirred for 24 h. Afterwards, the MWCNTs-Risp were isolated by ultracentrifugation, rinsed 3× and dried at 37 °C. Encapsulation efficacy (EE) and drug content (DC; theoretical value 25%) were measured with UV/VIS (λ=280 nm) by calculating the loss of drug after the loading procedure. Particle size distribution and zeta potential were evaluated by Nano-ZS. The in vitro release was studied through a dialysis membrane, in PBS pH 7.4 (at 37 °C). The drug release data were fitted into various mathematical models to determine the drug release kinetics. To find out the mechanism of drug release, 60% of drug release data was fitted in the Korsmeyer-Peppas (K-P) model.

RESULTS: EE was slightly higher in non-irradiated MWCNTs (79% vs. 73%), while similar values for DC (approx. 20%) were observed. Differences in surface charge (-22 mV vs. -34 mV) and average size (220 nm/PdI 0.39 vs. 740 nm/PdI 0.60) for non-irradiated and irradiated MWCNTs-Risp, accordingly, were determined. The cumulative percent of Risp release was similar for both formulations, being approx. 70% after 24 h. However, the initial burst release was higher in irradiated formulation, 21.6% vs. 9.6% after 2 h. The first order was the best fit model for the Risp release from the non-irradiated MWCNTs (R2=0.999; k=0.05 h^{-1}), while for irradiated formulation, a square root one (R2=0.999; kH=13.7 $h^{-1/2}$). The "n" for the K-P model was between 0.45 and 0.89, indicating non-Fickian diffusion in drug release.

CONCLUSION: Risp loaded MWCNTs were prepared, with capability to sustain Risp release rate. The exposition of the MWCNTs to X-ray irradiation affected their physicochemical properties. Significantly higher burst release was observed during the first 2 h, indicating more loosely drug attached to the surface of the irradiated MWCNTs.

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P7/5

Functionalized MWCNTs as etoposide carriers: characterization and release kinetics

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INTRODUCTION: Multi-walled CNTs (MWCNTs) were produced as etoposide (Eto) carriers and functionalized by maleic acid anhydride (MA-MWCNTs) and polyethylene glycol 1500 (PEG-MWCNTs) to enhance their biocompatibility, encapsulation tendency and modify drug release. Maleic acid copolymers have been already known by their antitumor activity, while PEG for providing optimal half-life circulation time, high uptake in tumors and low in other cells [1]. The aim of the study was to characterize these f-MWCNTs for their physicochemical properties and in vitro drug release.

MATERIALS AND METHODS: MWCNTs were previously prepared, functionalized and adequately characterized [2]. Solution of Eto in DMSO/water was added to the f-MWCNTs and the dispersion was stirred for 24 h. Afterwards,

the f-MWCNTs-Eto were isolated by ultracentrifugation, rinsed 3× and dried at 37 °C (48 h). Encapsulation efficacy (EE) and drug content (DC) were measured with UV/VIS (λ=282 nm) by calculating the loss of Eto after the loading procedure. Particle size distribution and zeta potential were evaluated by Nano-ZS. The in vitro release from all series was studied through a dialysis membrane, in PBS pH 7.4 as a dissolution medium, at 37 °C. The drug release data were fitted into various mathematical models to determine the drug release kinetics. To find out the mechanism of drug release, 60% of drug release data was fitted in the Korsmeyer-Peppas (K-P) model.

Results: EE for the formulations was between 56% (MWCNTs-Eto) and 60% (PEG-MWCNTs-Eto). High DC was achieved, being between 15% and 17% (theoretical 25%), respectively. Negatively charged MWCNTs were produced [-19 mV (MA-MWCNTs-Eto) and -25 mV (MWCNT-Eto)], with average size from 191 nm (MA-MWCNTs-Eto) to 280 nm (PEG-MWCNTs-Eto). The cumulative percent of Eto release was between 81% (MWCNTs-Eto) and 71% (PEG-MWCNTs-Eto) after 24 h. All formulations showed an initial burst release and prolonged release in the later stage. For the formulations, the best fit model was first order. The "n" exponent for K-P model was between 0.45 and 0.89, indicating non-Fickian diffusion mechanism in drug release.

CONCLUSION: Eto loaded MWCNTs were prepared, with suitable physicochemical properties and capability to sustain Eto release rate. The functionalization of MWCNTs showed potential to increase drug loading and slow down drug release.

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P7/6

Optimization of the production process and product quality of titanate nanotube-drug composites

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INTRODUCTION: Nanotechnology has its fundamental impact in developing all areas of science, especially in drug formulation and delivery, which is known as nanopharmaceutics. Moreover, conventional drugs often have poor pharmacokinetic and biopharmaceutical properties and other problems such as poor stability, toxicity, poor solubility in aqueous media and poor bioavailability [1]. Whereas, nanotechnology-based drug delivery systems may enhance shelf-life and acceptability by increasing either uptake efficacy or patient compliance [2]. Furthermore, nanotechnological methods may help to improve the solubility, absorption, bioavailability, and stability of drug molecules [1].

MATERIALS AND METHODS: Titanate nanotubes (TNTs) were synthesized with a hydrothermal method, and then composites were formed with atenolol (ATN) and hydrochlorothiazide (HCT) using various solvents. Ethanol, methanol and 0.01M HCl solution or ethanol and 1M NaOH solution were used to produce TiATN and TiHCT composites, respectively. The physicochemical properties of the samples were investigated by using TEM (FEI, OR, USA) and SEM (Hitachi, Japan) imaging to analyze the texture, optical contact angle tester (DataPhysics GmbH, Germany) to determine the surface free energy, FT-IR spectrometer (Thermo Fisher Scientific Ltd., MA, USA) and DSC/TG apparatus (Mettler-Toledo Ltd, Hungary) to detect the interaction between drugs and TNTs.

RESULTS: The results revealed that the strength of interactions is highly connected to the solubility of the drug in the applied solvent. According to SEM and TEM pictures, a strong recrystallization of the drug is observable from a worse solvent. This phenomenon acts negatively on the strength of interactions, which was supported by the results of the spectroscopic and DSC/TG measurements. The strength of interactions also exhibited considerable influence on the surface characteristics of the products, which basically determines their processability and their behavior in a biological environment.

CONCLUSION: TiATN and TiHCT composites were successfully prepared by using HCL 0.01M and NaOH 1M as solvents, respectively, which suggests that the selection of the appropriate solvent will basically determine the effectiveness of the composite formation process and product quality.

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P7/7

Preparation and characterization of cell culture controllable, marker incorporating liposomal formulations

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INTRODUCTION: Liposomes, a type of nano-delivery systems, are used for targeted drug delivery [1]. Nowadays, the main intention of nanotechnological researches is to provide new therapeutic and diagnostic options and alternate routes for drug delivery besides the conventional intravenous method.

The aim of our research project is to find a possible method for the administration of adenosine triphosphate (ATP) into human body through liposomal formulations [2] to treat acute pancreatitis.

The objectives of this work is to create formulations made from the proper liposomal wall contents, incorporate propidium iodide, a cell dye as a marker, then ATP molecule as a biologically active substance into liposomes.

MATERIALS AND METHODS: Propidium iodide containing liposomes were designed and the formulations were prepared by thin-film hydration method. Instrumental investigations were conducted. Particle size distribution was determined via dynamic light scattering technique. Zeta potential was verified to check the charge of the vesicular surface. Drug incorporation capacity and cell penetration ability was measured through propidium iodide cell dye incorporation into liposomes and using fluorescence microscopy. Cell penetration was surveyed on human embryonic kidney 293T cell line.

RESULTS: Liposomal formulations were prepared with vesicles under 100 nm from different combinations of wall contents. Most of the measured zeta potential values were slightly negative. The products were tested on cell cultures beside drug incorporation capacity and cell penetrating ability measurements. Our results confirmed that the liposomal formulations are able to penetrate pancreatic cells.

CONCLUSION: Due to the utilization of propidium iodide marker we were able to test the cell penetrating ability of our formulations. We would like to prepare further, pancreatic cell penetrating and ATP molecule containing liposomal formulations. Examination of other nano-delivery systems could broaden our opportunities.

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P7/8

Co-delivery of curcumin and doxorubicin in PEGylated liposomes enhances their therapeutic potential against colon cancer

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INTRODUCTION: Tumor-targeted co-delivery of the cytotoxic agents and natural compounds might be a valuable strategy to improve their antitumor activity and to lower the extent of the side effects. Our previous studies have shown that curcumin (CURC) and doxorubicin (DOX) co-encapsulation in long circulating liposomes (LCL-CURC-DOX) determines synergistic inhibitory effects on C26 carcinoma cell proliferation [1, 2]. In

the current study, the physico-chemical and biological properties, as well as the antitumor activity in C26 colon carcinoma bearing mice were explored, for an optimized LCL-CURC-DOX formulation.

MATERIALS AND METHODS: Optimized LCL-CURC-DOX were prepared and characterized in terms of size, surface charge, drug loading, in vitro drug release, hemolityc activity and stability in simulated biological fluids. Further, treatments consisting of LCL-CURC (5 mg/kg), LCL-DOX (2.5 mg/kg), LCL-CURC-DOX (5 mg/kg, 2.5 mg/kg) or free drugs at equivalent doses, were i.v. administered at day 7 and 10 after C26 cell inoculationin mice, and their effects on tumor growth were evaluated. The mechanisms responsible for this antitumor activity were evaluated through markers specific for supportive processes in tumor microenvironment such as inflammation, invasion and apoptosis.

RESULTS: LCL-CURC-DOX had appropriate physico-chemical properties for i.v. administration, were stable in simulated biological fluids and hemocompatible. This formulation demonstrated the highest antitumor efficacy among all treatment tested. The antineoplastic effects were due to inhibition of the activity of the transcription factors, NF-kB and AP-1, and to alteration of Th1/Th2 cytokine balance in TME, in favor of the Th1 arm.

CONCLUSION: Our results proved that the developed nanoformulation, based on the co-encapsulation of CURC and DOX in long-circulating liposomes, met the requirements of a modern drug delivery system for future colorectal cancer therapy.

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P7/9

Chitosan/sodium lauryl ether sulfate microcapsules as carriers for vitamin E: in vitro release study

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INTRODUCTION: The important current focus in production of cosmetics is usage of vitamin E (E), a natural antioxidant protective for tissues from UV radiation, delays photoaging and provide moisturizing effect. Encapsulation is needed for its protection from high temperature, oxygen, and light, during storage, and also for a potential ability to control its release and delivery. Preparation of microcapsules of desired characteristics depends on various factors (size and nature of the core substance, wall material, techniques and parameters of encapsulation) [1, 2]. The study aimed to evaluate chitosan/sodium lauryl ether sulfate (Ch/SLES) microcapsules with E as a delivery system for skin care.

MATERIALS AND METHODS: Microcapsules were prepared by complex coacervation. Initially, a 20% O/W emulsion with E (10% solution in medium-chain triglycerides), stabilized with the mixture of Ch (0.1 %) and SLES [3], was obtained by Ultra Turrax T25 homogenization. The emulsion, without or with a crosslinker, formaldehyde (FA) or glutaraldehyde (GA), was spray dried. The in vitro release profile of E from the microcapsule samples (0.1 g) was studied in 100 g of ethanol 80%, under continuous stirring at room temperature. The dissolved E in supernatant aliquots (2 ml) was analyzed during 90 min, by the Halo DB-20S UV-VIS spectrophotometer.

RESULTS: The obtained release profiles were analyzed by fitting in different mathematical models and in all samples correlate the best with Korsmeyer-Peppas model. The diffusion exponent n values (0.05-0.23) indicated non-Fickian diffusion. We assumed that release of E was based on a combination of rinsing from the surface of the microcapsules [4] and diffusion through the capsule wall. For microparticles with GA, n was the lowest, the release was rapid and the amount of release of the substance was higher (i.e., more pronounced rinsing process), compared with FA and microcapsules without the crosslinker, where release of E was more controlled by diffusion.

CONCLUSION: E vitamin release from Ch/SLES microcapsules followed Korsmeyer-Peppas kinetics. The selection of the crosslinker influenced their surface properties, the surface amount

and permeability of the capsule wall for E vitamine diffusion.

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Determination of the protein corona stability complex of nanoliposomes in physiological mediums

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INTRODUCTION: Due to nanosizing results in the creation of new interfaces and in a positive Gibbs free energy change, nanoliposomal dispersion is a thermodynamically unstable system with tendency of agglomeration or vesical growth. Also, upon the addition of nanoliposomes (NLs) to biological fluids, there is an almost immediate fouling of their surfaces with proteins and other cellular apparatus forming a layer known as protein corona (PC), which determines the eventual properties of NLs [1].

MATERIALS AND METHODS: In order to investigate the effect of LIPOID PE 18:0/18:0-PEG 2000 (PEG) on the in vitro stability of NLs and PC complex formation, two formulations (lechitin: cholesterol:PEG = 8.7:1:1.7 and 9:1:0.17 for S1 and S2, respectively) loaded with rosmarinic extract were prepared by the modified lipid film hydration technique [2]. Prepared NLs (200 μl) were incubated in 800 μl phosphate buffer pH 7.4 or human plasma at 37 OC for 2, 6 and 24h and analyzed in terms of particle size, particle size distribution and zeta potential (Zetasizer Nano-Series, Malvern Instr. Ltd., UK).

RESULTS: In physiological relevant medium with pH 7.4, the diameter (D) of freshly prepared NLs was 107.2 and 113.7 nm with a relatively narrow size distribution (PDI~0.27) and zeta-average of -18.5 and -45.1 mV, for S1 and S2, respectively. No significant differences were observed during the examined period of 24h. Obtained results showed that the concentration of PEG influenced the mean size and zeta potential of NLs. In human plasma, D of NLs was 111 and 123.6 nm with PDI=0.3 and zeta-average of -18.5 and -17.5 mV. S1 was stable during the period of 24h. In opposite, during the examination period of 24h, S2 showed slight reduction in the zeta potential (- 16.7 mV during first 2 h). After 6 h and gradually onto 24 h, the zeta potential became more negative (-20 mV). This could be due to PC complex formation. In late time intervals, probably there was a displacement of the plasma proteins present onto hard corona layer and formation of soft corona complex with the NLs [1].

CONCLUSION: Due to the steric stabilization, NL formulation prepared with sufficient amount of PEG showed satisfactory stability in relevant mediums and potential for prolonged circulation time, thus enabling effective drug deposition to the target site.

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P7/11

Low-energy nanoemulsions with antioxidant red raspberry seed oil and fruit extracts – Influence of extract type and its quality and different polyols on EPI nanoemulsion formation and stability

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INTRODUCTION: Red raspberry seed oil is a rich source of anti-inflammatory polyunsaturated fatty acids and antioxidants while hydro-glycolic extracts made from raspberry fruit are known for carotenoids, vitamin C and tannins. To use their biological potential in effective skin care products we formulated low energy nanoemulsions (LE-

NEs) as prospective carriers for unstable molecules.

MATERIALS AND METHODS: LE-NEs were prepared using Emulsion Phase Inversion Method (EPI) at room temperature (RT). LE-NE region was detected by phase diagram study with Polysorbate 80 as a surfactant, red raspberry seed oil extracts (RO) as oil phase with added Tocopheryl acetate of varied concentrations (costabilizer) and water titrated in small aliquots to surfactant-oil mixtures. We tested 4 different RO (cold pressed-refined, -unrefined, CO2-organic and non-organic). The influence of polyols (glycerol, propylene glycol, butylene glycol, pentylene glycol) as cosurfactants and antioxidant hydro-glycolic fruit extracts (Red raspberry–RE and French oak–FE) was investigated by varying concentrations in the water phase. The NEs were confirmed visually, by DLS (droplet size and PDI), pH and conductivity measurements, polarized light (PLM) and optical microscopy (OM). All stable NEs were kept at RT and retested monthly, up to 3 months. Antioxidant activity of the selected samples was confirmed by ß-carotene-linoleic acid assay, while DPPH one interfered with the NE structure.

RESULTS: SOR and SER were the same for all 4 types or RO extracts (NEs droplet sizes: 120 to 150 nm, PDI = 0.1). The most crucial parameter for NEs formation and stability was the type of RO extract since PLM and OM revealed the presence of large structures (10-20 μm) undetected by DLS measurements in NEs prepared with CO2 RO extract organic. It was found that the polyol type and concentration should be specifically adjusted for each RO extract, while glycerol was the only one suitable for all 4 oils. Addition of antioxidant extracts (RE, FE) to the water phase improved antioxidant activity of LE-NEs.

CONCLUSION: LE-NEs are promising carriers due to low energy production/inexpensive equipment, with very complex structure affected by the minimal composition changes such as the ones we observed employing natural extracts of the same INCI name but supplied from different sources.

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P7/12

Lecithin-based low-energy nanoemulsions with eucalyptol as a co-stabilizer: interfacial phenomena examination by electron paramagnetic resonance spectroscopy

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INTRODUCTION: Owing to the physicochemical and biological benefits associated with their structure, and a palette of possible applications, there is a growing interest in the biocompatible nanostructured vehicles intended for the use in pharmaceutical, cosmetic and food industry. Low-energy nanoemulsions (LE-NEs) could be posted among other colloidal vehicles that have emerged. However, apart from confirmed advantages, safety aspects should be considered due to the surfactants used as stabilizing agents. With the view to lowering the surfactant content, eucalyptol (EUC), well established penetration enhancer, solvent, fragrance and taste modifier, was tested in terms of its effects to the interfacial properties of selected LE-NEs.

MATERIALS AND METHODS: LE-NEs with different surfactant-to-oil ratios (SORs) were formulated applying spontaneous emulsification as a preparation technique, using medium-chain triglycerides (MCT) or a mixture of MCT and EUC (1:1) as the oil phase, and a combination of soybean lecithin and polysorbate 80 (1:9) as stabilizers. Droplet size analysis was conducted via dynamic light scattering and laser diffraction. An insight to the interfacial properties of selected LE-NEs was realized through electron paramagnetic resonance spectroscopy (EPR), using 5-doxyl stearic acid (5-DSA) as a spin probe.

RESULTS: With regard to the finding that SOR is an important formulation parameter for LE-NE preparation, displacement of MCT with EUC played a significant role in this process. The lowest SOR value able to give the LE-NE for the system with MCT was 0.75, whereas, in case of MCT-EUC blend, it was 0.3. Additionally, LE-NEs with

EUC exhibited significantly lower mean droplet size compared to those without terpene. EPR experiment reflected the extent of the interfacial membrane rigidity/flexibility at the microenvironment of the spin probe. A significant increase in the mobility of 5-DSA was observed in the formulation with EUC, suggesting that interfacial flexibility exhibited prominent influence on the LE-NE formation.

CONCLUSION: Presence of EUC strongly affected the flexibility of the interface and significantly lowered the mean droplet size of the LE-NEs These results revealed the co-stabilizing ability of EUC. Additional assessment is needed to throw more light to potential interactions at the interface.

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P8- SOLID DOSAGE FORMS

P8/1

Enhancing particles mixing in cubic mixer using by baffles

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INTRODUCTION: Tumblers have been widely used in particle mixing due to many advantages such as, large handling capacity and there simple structure.

However, serious segregation phenomenon often appears when bidisperse or multi-disperse particles that differ largely in properties are mixed by the use of this kind of equipment.

Using baffles in the rotating drums is an effective method to improve the mixing quality, especially for cohesive materials.

The effect of cohesion strength and baffle length was investigated by Zhou et al [1] using DEM simulation method. Jiang et al [2] investegate the effect of baffles form and dimensions by numerical simulation.

In this work an experimental study was carried out to investegate the effect of baffles insertion on mixing performance in cubic mixer, for differentes experimentales conditions.

MATERIALS AND METHODS: Mohydrate lactose 200 M and micronized sodium bicarbonate were used as cohesive mixing system, to investigate the effect of a flat baffles (-) lenght in cubic mixer. The experimental conditions studied are the rotational speed (10 and 20 rpm) and the fill level (35 and 50% (v/v)) with top bottom loading profile. The mixing time and the RSD curves were used to caracterize the mixing homogeinity.

RESULTS: The baffle length played a significant role on mixing and the increase of baffles lenght enhanced mixing especially at 50% of fill level. On the other hand, at low fill level a shorter baffles are needed to get a good mixing. The increase of the rotationnel speed can be good for the mixing quality at 35% of fill level.

CONCLUSION: From the results it can be conclude that the baffles insertion enhance mixing performance for optimized conditions. And it depends strongly on the experimental conditions and baffles dimensions.

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P8/2

Measurement of the density distributions in ribbons containing paracetamol and various excipients by X-ray μCT and correlation to the minimum solid fraction

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INTRODUCTION: Dry granulation is often used when water sensitive APIs have to agglomerated and roller compaction is the preferred metod. However, compacts from this process often suffer from one disadvantage. Depending on the roll design the density distribution within the compacts differs from center towards the edge of the ribbons. This can lead to wider particle size distributions of the granules after subsequent milling. The presented work shows how density distributions of ribbons, measured by X-ray μCT, differ in correlation to the fillers used for their production.

MATERIALS AND METHODS: Formulations contained paracetamol (50%), croscarmellose sodium (2%), magnesium stearate (1%) in combination with fillers for direct compression (47%). The

filler types used were: anhydrous dibasic calcium phosphate, alpha-lactose monohydrate and microcrystalline cellulose. Roll comopaction was carried out on a Freund Vector TFC 220 compactor at varying roll speed (3 – 6 RPM) and compaction forces (10 kN to 30 kN) to yield ribbons of 2.0 thickness .X-ray μCT of specimens of about 2.5 cm in length were subjected to analysis by X-ray micro-computed tomography (CT alpha, Procon X-Ray, D).

RESULTS: Ribbons made with MCC were 25 mm wide if prepared at lower force and at higher force were close to 28 mm wide. Lactose ribbon width was found to be 23 mm and 26 mm respectively. Samples made with calcium phosphate were 22 mm to 26 mm wide. Solid fraction of the ribbons containing calcium phosphate were found to cover a wider range with a minimum solid fraction around 0.55 and a maximum at a solid fraction atf 0.87. Lactose ribbons have lower porosity (1- solid fraction) of 0.12 to 0.3 and MCC ribbons between 0.16 and 0.35.

Discussion: The "loss" on ribbon width could be attributed to two mechanisms. Firstly well flowing materials (lactose, calcium phosphate) are escaping the compaction zone due to poor sealing of the rolls while this effect is reduced at higher compaction speed. Secondly less compcatible materials are pre-compacted less by the feeding-auger, especially at low compaction speed.

CONCLUSION: Excipients of different compactibiilty and flowability have a siginfiicant impact on the quality attributes of the obtained ribbons.

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P8/3

Co-processing by fluid-bed melt granulation for improving tableting properties of lactose monohydrate

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INTRODUCTION: Direct compression is preferred method for tablet production due to its simplicity, the fewest processing steps and the lowest requirements for processing equipment. Since application of direct compression requires good flowability and compactibility of tableting mixture, it is of utmost importance to provide high excipients functionality in terms of flowability and compactibility [1]. This study was aimed to developed co-processed excipients, suitable for direct compression without need for addition of external lubricants, as they can adversely affect tablet mechanical properties, disintegration and drug release.

MATERIALS AND METHODS: Co-processing of mixture containing lactose monohydrate, calcium hydrogen phosphate dihydrate and croscarmellose sodium was performed by fluid-bed melt granulation using 10 or 20% of three different binders with lubricant properties: poloxamer 188, glyceryl palmitostearate and polyethylene glycol 4000. Obtained granulates were tested in terms of their flowability and particle size distribution, followed by testing tableting behaviour using Gamlen D-series dynamic powder compaction analyser (Gamlen Instruments, UK).

RESULTS: Granules of more uniform size were obtained with higher proportion of binder. Flowability of all prepared granules was significantly better compared to lactose monohydrate and commercial co-processed excipient Ludipress®. Lower work of compression for all co-processed mixtures, compared to Ludipress®, indicates on lower resistance of these mixtures to the applied compression force. Tablets prepared by compressing mixture granulated with 20% of polyethylene glycol 4000 and 20% of poloxamer 188 exhibited the highest tensile strength amongst all co-processed samples. Mixture granulated with 20% of poloxamer 188 showed more robust compression behaviour, i.e. tensile strength do not vary significantly with variation of the compression force. Co-processing with either of the binder significantly reduced adhesion of materials to the parts of tableting machine. Ejection stress lower than 5 MPa indicates on good lubricant properties of the prepared granulates and that it is not necessary to add external lubricants.

CONCLUSION: Co-processing by fluid-bed melt granulation was successfully used to prepare co-processed excipients suitable for direct compression without need for addition of external lubricants.

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P8/4

Self-organized criticality in granule flowability examinations

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INTRODUCTION: Self-organized criticality (SOC) phenomenon is a cardinal property of dynamical systems. Flow properties of powders and granules can be described by this theory in the pharmaceutics. These systems display a specific augmentation reaching a critical point where avalanche behavior of the particles can be observed. The complex behavior of these systems can be partly described with simple power laws [1].

MATERIALS AND METHODS: Different granulation sets were made with two dissimilar characteristic active pharmaceutical ingredients (paracetamol and prednisolone) according to our factorial design. Lactose, povidone, microcrystalline cellulose and talc were used as excipients (materials were supplied by Molar Chemicals Kft.). Examination of flow property (using ASTM funnel and a glass plate) was supplemented with a visual analysis. Professional camera (Canon EOS D1200) and a black background were applied. Flowing of the granules was recorded using 1280x720 resolution with 50 fps. Frames were extracted from the videos and analyzed (Carl Zeiss`s AxioVision) recording the appearing avalanches. Our results were compared to a hypothetical power law function. Angles of repose were measured too. Experimental and hypothetical relative frequency - avalanche size distribution functions were created to reveal the most important connections. Talcum as a potential influential material of the SOC behavior and flowability was examined.

RESULTS: Parameters of the hypothetical and experimental functions were calculated and compared. The experimental functions display cut off region and the distributions have an infinite mean. The characteristics of the active pharmaceutical ingredients can influence the scaling parameter of the function which can lead to changes in the flow properties, in the avalanche-effect. Smaller angles of repose were measured in case of granules containing paracetamol.

CONCLUSION: Diverging behavior of granule flowability from the ideal power law function can provide additional information during pharmaceutical formulation.

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P8/5

Effect of magnesium stearate on the physicochemical properties of co-processed lactose using compaction simulator.

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INTRODUCTION: Manufacturing the solid dosage form of an orally administered drug requires lubrication to enhance manufacturability, ensuring that critical quality attributes of the drug product are maintained during manufacture.[1] The effect of lubricant (Magnesium Stearate) on the compaction characteristics of a model drug (Ibuprofen DC 85) in combination with co-processed lactose based excipients (Cellactose® 80 and MicroceLac® 100) are studied.

MATERIALS AND METHODS: A study was designed to develop and optimize tablet formulations manufactured by direct compression. The formulations contained 200mg of Ibuprofen DC 85, varying proportions of Cellactose® 80 (75% alpha-lactose monohydrate and 25% powdered cellulose), MicroceLac® 100 (75% alpha-lactose monohydrate and 25% microcrystalline cellulose) and Magnesium Stearate in different concentrations. Tablets were produced at pressures between 46MPa and 274MPa using Stylcam Compaction Simulator with a 11.8 mm flat faced Euro B punch.

RESULTS: The lubricant sensitivity of the materials was determined using the R values (i.e. the ratio of the maximum lower punch force to the maximum upper punch force). It was seen to be the highest with the formulation containing Cellactose® 80 at 137 MPa.

Evaluation of ejection force and compaction pressure data demonstrates that there is improved ejection force as the lubricant concentration is increased until a plateau is reached.

The results obtained were evaluated and it was

revealed that the change in lubricant % has a direct effect on the tablet tensile strength. The drug compactability was improved with the mixture containing MicroceLac® 100 and the crushing strength was the highest when the lubricant amount was 0.5%.

CONCLUSION: The R values were closer to unity when the pressure applied was higher, this indicated increased efficiency of magnesium stearate as a tablet lubricant at higher pressures. Magnesium Stearate concentration was optimized at 0.5% using values obtained from tensile strength in order to enhance manufacturability without affecting disintegration and dissolution of the drug product.

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P8/6

Use of Compaction Simulator to Determine the Effect of Filler on the Compactability Characteristics of Paracetamol as a Model Drug

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INTRODUCTION: In this study the poor flowability and bad compressibility characteristics of the model drug were observed. Dry granulation can be used in order to change powder properties of paracetamol using slugging process which has positive impact on flowability and compressibility.

MATERIALS AND METHODS: Paracetamol (Tianjin Bofa Co.) was slugged (Korsh XP1) with punch diameter of 20mm, crushed and sieved using 0.68mm sieve size. The study was carried out to determine the use of two different fillers (Starlac® and Flowlac® 100). The approach used in this study entailed a series of tablet designs which were formulated by addition of active material with filler(s) in different concentrations and 2% Stearic Acid as lubricant. Tablets were compressed at different forces with different filler concentrations. Angle of repose, Carr's Index, Hausner Ratio, and flow rate were the physical and rheological properties of the powders that were evaluated. Stylcam (R200 Medel Pharm.) compaction simulator was used to produce tablets (11.8mm flat faced Euro B punch) and obtain compaction data at a range of pressures (105 MPa-205 MPa).

RESULTS AND DISCUSSION: The effects of tableting pressure on mechanical properties: thickness, friability, weight variation and crushing strength were evaluated in order to obtain the tabletability profile of the individual formulations. Tensile strength vs Compaction pressure was plotted and the results of Starlac® showed greater tensile strength at all compaction pressure points (at 205MPa tensile strengths for Starlac® and Flowlac® tablets was 1.2MPa and 0.8MPa respectively).

The compactibility of granulated Paracetamol was improved by the increase in concentration of filler (30-50%), hence tensile strength increased. Results obtained were evaluated using Force- Displacement curve in order to explain the compression phenomenon of the formulations.

CONCLUSION: The data produced by the compaction simulator supports that use of fillers improves the compactability characteristics of granulated paracetamol. Summarily, the findings revealed that Starlac® performed better in terms of powder, compaction and tabletting properties.

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P8/7

Effect of magnesium aluminometasilicates on compaction properties of pharmaceutical formulations

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INTRODUCTION: Many of the powder excipients, which are used in pharmaceutical industry, exhibit poor flow properties. Therefore, glidants are usually added into the powder mixtures to alleviate the flow problems. Despite their advantages in terms of improved flow, the presence of glidants affects the process of tablet compression, as well as final tablet strength or dissolution rate. Glidants affect the energy side of the compression due to the reduction of the friction within the powder or reducing required volume reduction. The tensile strength of tablets from binary mixtures containing glidant is in general decreased related to the strength of tablets prepared from the other excipient alone. The measured decrease of the tensile strength of the tablets is considered to be the result of reduced interparticle bonding.

MATERIALS AND METHODS: This work was focused on studying the influence of novel family of glidants - magnesium aluminometasilicates (Neusilin®). Several blends containing the model excipient (microcrystalline cellulose) and various magnesium aluminometasilicate grades were prepared. Their impact on tablet compression process was characterized using Gamlen GTP-1 compaction analyzer. The force – displacement data at various pressures were used for the evaluation. Sotax Multitest 50 was used for tensile strength determination. The effect of the glidants was studied in terms of its various grades, concentration and in terms of mixing time.

RESULTS: The results from force – displacement record revealed that certain parameters such as the punch detachement force and factor of elasticity are affected by mixing time, but there is no monotonous trend. Energy of plastic deformation increased at longer mixing time. The energy of plastic deformation and the factor of elasticity were also compared for different grades and concentrations of magnesium aluminometasilicate glidants. Concerning the tensile strength, all tested glidants affected the tablet strength value, but there was no significant dependence on mixing time.

CONCLUSION: The study compared the compression properties of microcrystalline cellulose blends containing Neusilin® family glidants. In general, those glidants affect the compression properties less than traditional colloidal silica glidants. This in combination with their good flow enhancing ability makes the tested magnesium aluminometasilicates suitable for using as glidants in formulations for direct tablet compression.

P8/8

Influence of the mechanical properties of dry binders on the tabletability

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INTRODUCTION: Dry binders are important for direct compression to ensure adequate tensile strength and friability of tablets. Dry binders are also necessary for roll compaction / dry granulation (RCDG) to reduce the fraction of fines [1]. A rational selection of dry binders would be desirable, to save costs and improving the robustness of tablets. A screening of dry binders in formulations with paracetamol identified efficient binders for roll compaction and tableting [2]. Now, the mechanical properties of binders were related to the tabletability of formulations containing 10% binder.

MATERIALS AND METHODS: HPC (HPC SSL SFP, Nippon Soda), COP (Kollidon VA64 F, BASF SE) and MCC (Vivapur 105, JRS Pharma) were used as dry binders. Tablets made of pure binders were compressed to 8 mm flat-faced tablets with a weight of 130 mg using a compaction simulator (Styl`One Evolution, Medelpharm). The compaction simulator was used to determine the breaking force of these tablets. Therefore, the tablets were radially compressed at compression speeds of 3.5 mm/s and 0.01 mm/s. Tablets made out of 89 % DCPA (DICAFOS A150, Budenheim), 10 % dry binders and 1% magnesium stearate were compressed to 8 mm flat-faced tablets with a weight of 200 mg using a rotary die press (Pressima, IMA Kilian, Germany).

RESULTS: Tablets made out of pure COP and MCC tablets tended to break, while tablets made out of HPC were deformed to new compacts without breakage. Furthermore, a viscoelastic behaviour is obvious, due to the lower development of strength at a slower compaction speed for HPC. These findings can be connected to the tabletability of DCPA-based tablets. HPC generated at lower pressures relative high tensile strengths, while the tabletability was lower at higher pressures compared to MCC and COP. HPC is softer than COP and MCC, which provides rather strong compacts at lower pressures. This might also be the reason, why HPC was most suitable for RCDG (2), because the pressure during RCDG is comparably low.

CONCLUSION: Force-displacement curves of tablets made out of pure binders were analysed and related to tabletability plots, to gain a deeper understanding of the binding behaviour of dry binders.

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P8/9

Evaluation of excipients and processing agents intended for the compression of pellets into tablets

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INTRODUCTION: Efficient compression of coated pellets is a formidable task developed long since due to the considerable forces involved during procedures, the obstacle of segregation while mixing, as well as the rather frail nature of the coating. [1] Solving the relevant issues, however, could provide us with an easy-to-use and flexible dosage form possessing many therapeutical advantages, such as multiple-unit pellet systems (MUPS). [2] Using filler materials, such as microcrystalline cellulose (MCC) and a hydrophobic emulgent the formulation of a cushioning processing agent designed to mix freely with drug-containing pellets and able to prevent damage to pellet coating was proposed.

MATERIALS AND METHODS: Multiparticulate tablets containing model drug (potassium chloride) were prepared from filler materials, with the incorporation of hydroxypropyl-methylcellulose binding agent and V/O emulgent. Texture analysis and physical characterisation of excipients were conducted, while homogeneity of compressed tablets was determined by imaging techniques (microscopy, microfocus X-ray). Damage to pellet coating was examined via drug release test.

RESULTS: Texture analysis showed the novel processing aid rating the highest in plasticity. Moreover, the drug dissolution profile was not altered significantly after compression based on similarity (f2 value) evaluation. Homogeneous tablets could be prepared from multiple formulations, while only the ones made with the formulated cushioning agent were in accordance with the regulations of Ph. Eur. 8.

CONCLUSION: The results of this study show that the formulation of a cushioning excipient able to protect the pellet coating while mixing homogeneously is possible. Further adjustment, incorporating additional materials could provide manufacturers with a reliable, cost-effective method to produce pellets in tablet dosage forms.

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P8/10

Effect of the compression speed on the mechanical properties of co-processed excipients for direct compression

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INTRODUCTION: Co-processed excipients (CPEs) are combinations of two or more excipients that possess superior properties compared to the physical mixture of same combination of excipients [1]. Effects of two meltable binders, Compritol® 888 ATO (COM) and polyethylene glycol 4000 (PEG 4000), and compression speed on the mechanical properties of CPEs prepared by the melt-granulation were investigated in this study.

MATERIALS AND METHODS: CPEs were composed of lactose monohydrate (70%), calcium-hydrogen phosphate (15%), sodium starch glycolate (5%) and 10% of the meltable binder (PEG 4000 or COM for co-processed excipient A or B, respectively). CPEs were made by the melt-granulation, and compared to the physical mixtures of the same composition. Tableting properties were compared by powder compaction analyzer under the compaction pressure of 104 MPa at different speeds (60 mm/min, 80 mm/min and 100 mm/min). Properties of materials were estimated by calculating the tensile strength, porosity, detachment and ejection stress.

RESULTS: CPEs have demonstrated different mechanical properties in comparison to the physical mixtures. Co-processed excipient A (CPEA) in comparison to the co-processed excipient B (CPEB), had higher tensile strength (1,05-1,21 vs. 0,75-0,81 MPa), detachment (1,27-4,53 vs. 0,59-2,20 MPa) and ejection stress (1,94-6,05 vs. 1,22-2,57 MPa). The tensile strength of tablets made of CPEA (1,05-1,21 MPa) and physical mixture of the same composition (0,85-1,08 MPa) has increased with compression speed. The optimal compres-

sion speed, based on the values of detachment and ejection stress, was found to be 80 mm/min. CPEB demonstrated superior mechanical properties in comparison to the physical mixture of the same composition at compression speed of 80 mm/min. With the increase in compression speed the porosity of tablets made of physical mixtures have decreased, whereas in the case of CPEA and CPEB lower values of porosity are noticed at 80 mm/min.

CONCLUSION: Mechanical properties of directly compressible co-processed excipients prepared by the melt granulation method are influenced by the compression speed. Excipient co-processed with PEG 4000 has superior mechanical properties in comparison to COM used as the meltable binder.

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P8/11

Influence of different type of tabletting machine on process tableting co-processed excipient mannitol/maltodextrine

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INTRODUCTION: Designing a robust process of tabletting which can be transferred onto different tabletting presses can be very challenging. This study investigates the influence of different types of tabletting machines on the resulting parameters which closely describe tabletting process.

MATERIALS AND METHODS: For the production of tablets mannitol granulated with 5% maltodextrin and 1% of magnesium stearate were used. Process tabletting was performed on rotary tablet press simulator, Stylcam 200R, using four simulations of different tabletting machines (Killian Pressima, Fette P2000, Kilian Synthesis 330 and Kilian Synthesis s250). Tablet compression was performed using compression force 12 kN and Stylcam speed 35 rpm. Following responses were observed: upper punch force, upper punch displacement, as a graphical presentation using „Stylcam 200R" software. Comparison of real dwell time, real relaxation time, ejection force and simulated tabletting speed was also performed.

RESULTS: During tabletting process, capping was observed only when simulating KSynthesis 330. Based on responses comparisons, it can be observed that various differences between compaction profiles exist, especially between Pressima and Fette P200 on the one side and KSynthesis 330 and s250 on the other side.

KSynthesis 330 simulation resulted in shortest dwell time, and highest ejection force due to the highest simulated speed. The shortest compression time and the relaxation time before the next compression cycle exposed tablets to higher stress which lead to capping. This study confirmed that difference in compaction events can affect process performance: consolidation, dwell and relaxation. Therefore it is important to assess which tabletting speed is working for a given formulation and a tabletting machine, in order to avoid problems during scale-up.

CONCLUSION: This study proved to be useful as it provided additional knowledge regarding tabetting process development. Based on presented results, it could be concluded that transfer process tabletting can be performed easily from Pressima to Fette P200, KSyntesis s250 and for KSyntesis 330 some additional considerations are necessary to assess if the scale-up would be possible [1].

ACKNOWLEDGEMENTS:

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P8/12

Comparison of Orodispersible Minitablets Based on galenIQ™721 For Pediatric Use

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INTRODUCTION: Acceptance studies approved the benefit of orodispersible Minitablets (ODMT)

for the treatment of pediatrics [1]. There is already literature about ODMT based on Ludiflash® [2, 3]. Isomalt (galenIQ™721) is known for advantages in technological respect but also in physicochemical regard [4, 5]. The aim of this study was to determine the feasibility of galenIQ™721 as an excipient for ODMT in comparison to established Ludiflash®-Formulations. Hydrochlorothiazide (HCT) and Enalapril (EM) were chosen as model APIs, as these drugs are listed in the WHO List of Essential Medicines for Children [6].

MATERIALS AND METHODS: Minitablets based on galenIQ™721 (BENEO-Palatinit) or Ludiflash® (BASF) were compressed on a rotary die press Pressima (IMA-Kilian) using a 19-tip 2 mm punch. Drug load of 30.8 % HCT and 16 % EM was chosen. ODMTs were analyzed regarding their tensile strength, disintegration time with a modified method [2], content uniformity according to Ph.Eur. 2.9.6. Dissolution studies were performed in demineralized water with a basket apparatus stirred at 50 rpm using a UV-Probe by Ocean Optics USB4000.

RESULTS: ODMTs based on galenIQ™721 were developed successfully and can be compared to ODMTs based on Ludiflash®. Mechanical properties of the ODMT were acceptable and content uniformity was accomplished. Regarding the disintegration time, all of the ODMTs disintegrate within 30 sec and fulfill the requirements of the Ph.Eur. and FDA. The dissolution studies show a plateau for EM after 3 min and HCT after 13 min for ODMTs based on galenIQ™721 indicating full drug release. The difference in these dissolution profiles can be explained with the drug load, dissolution rate and solubility of the used APIs in water.

CONCLUSION: The development of ODMT with galenIQ™721 was feasible and comparable to established ODMT-formulations with Ludiflash®. The excipient galenIQ™721 seems to be suitable for the production of ODMT.

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P8/13

Formulation and characterization of lurasidone hydrochloride orally disintegrating tablets

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INTRODUCTION: Lurasidone hydrochloride (LRS HCl) is an atypical antipsychotic drug used for the treatment of schizophrenia and bipolar depression. Compliance of patients suffering from mental illnesses often poses a significant problem making administration and dosing of a drug quite challenging. In order to facilitate drug administration, a novel oral drug delivery system, an orally disintegrating tablet (ODT) of lurasidone hydrochloride has been prepared and characterized within this research. This type of tablet disintegrates in the oral cavity before swallowing in less than 3 minutes [1].

MATERIALS AND METHODS: Various tabletting mixtures have been prepared by melt granulation technique using Uni-Glatt (Glatt GmbH, Germany) fluid bed granulator. Mixtures were compressed to 8 mm diameter tablets using TDP-5T single punch tablet press (Zhejiang, China). Following materials were used: mannitol (MAN), microcrystalline cellulose (MCC) PH102, lactose anhydrous, croscarmellose sodium (CS), polyethylene glycol (PEG) 4000, magnesium stearate (MS) and lurasidone hydrochloride (LRS HCl). Mass and hardness uniformity and disintegration tests were performed in order to determine the optimal formulation parameters. Content uniformity and dissolution tests were carried out to study the effect of croscarmellose sodium (a superdisintegrant) on tablet disintegration rate and solubility of LRS HCl. Drug content has been determined using an appropriate UV/Vis spectrophotometric method. The effect of superdisintegrant addition method (in-situ or spray-coating method) has been studied as well.

RESULTS: Tablets produced using combination of mannitol and microcrystalline cellulose proved to have the most favorable ratio of hardness and

disintegration time. Therefore, such combination of excipients was used in the experiments in which LRS HCl was embedded in the tabletting mixture. Content uniformity test has shown significant deviation from the target value in tablets produced using in-situ addition method. Dissolution profiles show a slight increase in drug solubility in tablets where superdisintegrant was used.

CONCLUSION: Tablets in which superdisintegrant was added by in-situ method show the lowest disintegration time. When compared to other formulations, a slight increase in drug solubility was noticed as well.

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P8/14

Characterization of tableting properties for hot melt coated granules

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INTRODUCTION: Granules, as intermediate product in the preparation of tablets, can be compressed uncoated or after coating. Hot melt coating (HMC) is a novel technique which has numerous advantages in comparison to conventional coating methods [1]. Lipid coating of HMC granules can modify drug release, mask bitter taste of a drug substance and influence granules tableting properties [2]. The aim of this study was to investigate tableting properties of paracetamol granules coated with glycerol distearate (Precirol® ATO5).

MATERIALS AND METHODS: HMC paracetamol granules obtained in a modified fluid-bed apparatus (Mycrolab fluid bed system, Hüttlin, Germany) under different process parameters setups (15 samples), uncoated granules and physical mixture of granules ingredients were compressed using Gamlen D series (Gamlen Instruments Ltd, UK) at the compaction loads of 100-500 kg. Work of compaction, elastic recovery, tensile strength and ejection stress were calculated from the instrument generated data. Tablets hardness was tested using Erweka tablet hardness tester TBH125D (Erweka GmbH, Germany). All measurements were done in triplicate.

RESULTS: The work of compaction revealed favourable compression characteristics of the coated granules and physical mixture, but physical mixture showed poor compactibility as indicated by increased elastic recovery and low tablets hardness. Tablets obtained from HMC granules showed increased tensile strength in comparison to the uncoated granules and physical mixture. Also, tablets made of HMC granules exhibited significantly lower ejection stress (less than 1 MPa for all samples) than those made of uncoated granules, demonstrating good lubrication.

CONCLUSIONS: The estimated tensile strength, as well as the ejection stress indicated advantageous tableting properties of HMC granules in comparison to the uncoated granules and physical mixture of granules ingredients. Additional advantage of the investigated HMC granules is that compression and ejection processes do not require the addition of external lubricant due to lubricant property of Precirol® ATO5.

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P8/15

Evaluation of physicochemical and tableting properties of rutin-cyclodextrin complexes

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INTRODUCTION: Rutin is a flavonoid, commonly used as an anti-inflammatory, antimicrobial and antioxidant active agent. Rutin is poorly water soluble and has low bioavailability. One of the approaches employed to improve solubility and bioavailability of drugs is by combining them with cyclodextrins (CD). CD are cyclic oligosaccharides which are recognized as useful pharmaceutical solubilizers, able to increase solubility and oral bioavailability.

The aim of the study was to prepare and characterize the physicochemical and micromeritic properties of rutin-β-cyclodextrin and rutin-hydroxypropyl-β-cyclodextrin complexes with a subsequent feasibility study on tableting.

MATERIALS AND METHODS: Complexes were prepared by kneading and co-grinding methods in the molar ratio of 1:2 (rutin:CD).

Characterization of systems by using spectral (FT-IR, XRPD) and thermal (DSC) methods was carried out.

To obtain rutin-CD tablets, a direct compression method was used. Properties such as hardness and porosity were examined. Tabletability, compressibility and compactibility profiles were established. Also disintegration and dissolution tests for tablets were performed.

RESULTS: Analysis of the rutin-CD systems by XRPD, FT-IR and DSC showed a considerable degree of interaction between rutin and ß-CD or HP-ß-CD. The prepared tablets were flat, pale yellow in color and had smooth texture without any cracks. Tablets disintegrated by dissolution within the required time (below 15 min). Dissolution rates were higher for rutin-CD systems compared to pure rutin.

CONCLUSIONS: Cyclodextrins are good excipients for improving the biopharmaceutical properties of rutin. Their characteristics lead to the formation of complexes and tablets with better dissolution performance of the active.

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P9- QUALITY BY DESIGN AND IN-SILICO MODELLING

P9/1

In silico and experimental evaluation of solubility and lipophilicity of new succinimide derivatives

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INTRODUCTION: In the early stage of drug selection it is highly important to determine solubility and permeability (depending strongly on molecules lipophilicity) since over 85% of drugs on the market are applied orally.

MATERIAL AND METHODS: RP TLC was used for study of the retention behavior of N-(3- or 4- substituted phenyl)-2-methyl-2-ethyl-succinimide derivatives. Precoated RP-18W/UV254 10×10 cm plates (Macherey-Nagel GmbH and Co., Düren, Germany) were used as stationary phase and binary solutions of water with acetone with a varying volume fraction, ϕ of organic solvent, were the mobile phase. After development, the spots were detected at 254 nm with UV lamp and Rf values were measured. For each compound analyzed, logS (logarithm of solubility) and logD values (log of the distribution coefficient of the compound at pH=7.4) were determined by the usage of acdlabs software.

RESULTS: Retardation factor, RM was calculated for each compound of 11 analyzed compounds according to the equation: RM=log(1/Rf-1). In the linear correlation of the RM values versus ϕ, the chromatographic retention constant RM0 was obtained as extrapolated value to 0% point: RM=RM0+S×ϕ. Statistically significant linear correlation was observed between retention constants RM0 and logS and logD (r^2=0.962, $p<0.001$ and r^2=0.954, $p<0.001$, respectively) for the investigated compounds.

CONCLUSIONS: Experimentally obtained retention constants may be used as alternative method determining lipophilicity. Retention constants values increase with the increment of logD and with the decrement of logS. All analyzed compounds have desirable solubility and lipophilicity.

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P9/2

Correlation of experimentally determined lipophilicity with in silico compartmental distribution of new succinimide derivatives

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INTRODUCTION: High attrition rate of potential drug candidates with undesirable pharmacokinetic profile requires determining of pharmacokinetic behavior in the earliest stages of drug candidates selection [1].

MATERIAL AND METHODS: Retention behavior of N-(3- or 4- substituted phenyl)-2-methyl-2-ethyl-succinimide derivatives was observed by applieng RP TLC method. As stationary phase precoated RP-18W/UV254 10×10 cm plates (Macherey-Nagel GmbH and Co., Düren, Germany) were used while mobile phase was binary solutions of water with acetone (varying volume fraction, ϕ of organic solvent). The spots were detected at 254 nm with UV lamp and Rf values were measured. For each compound analyzed, volume of distribution, Vd (L/kg) and plasma protein binding, PPB (%) were determined by the usage of acdlabs software.

RESULTS: For each investigated compound retardation factor, RM was calculated by application of the formula: RM=log(1/Rf-1). When RM values were correlated versus ϕ, the chromatographic retention constants RM0 was calculated after extrapolating to 0% point: RM=RM0+S×ϕ. Linear correlation was determined between retention constants RM0 and Vd (r^2=0.941, $p<0.001$) while U-shape correlation was found between RM0 and PPB (r^2=0.779, $p<0.001$) for the compounds analyzed.

CONCLUSIONS: Volume of distribution of the compounds analyzed strongly depends on the molecules lipophilicity while affinity for binding for plasma proteins first decreases with increment of lipophilicity (and decrement of acidity) down to some point when it starts to increase described with U-shaped correlation. All compounds investigated have desirable volume of distribution and affinity for plasma proteins.

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P9/3

Mechanistic interpretation of inhaled budesonide deposition and absorption in rats using in silico tools

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INTRODUCTION: Inhalation products have received much attention in recent years [1], but the lack of adequate testing methods hampered the development of new formulations. In this context, in silico physiological modeling may faciliate this process. The purpose of this study was to investigate the ability of in silico simulation tools to predict deposition and absorption of inhaled aerosols, using budesonide as a model drug and rat model physiology.

MATERIALS AND METHODS: In silico modeling tools included MPPD model (v. 3.04, ARA Inc, USA) for the prediction of drug deposition in the lungs and GastroPlusTM software (v. 9.0.0007, Simulation Plus Inc, USA) to estimate budesonide absorption profile. The necessary input parameters were obtained from literature or in silico estimated. Model predictability was assesed by comparison with the in vivo data [2, 3].

RESULTS: The applied simulation strategy resulted in the (i) design of two compartmental model that adequately describes budesonide absorption after intravenous and oral administration; (ii) design and exploration of inhalation model in terms of identifying the key parameters affecting the drug bioperformance. The results indicated that small lung fluid volume and low drug solubility may be the limiting factors for budesonide dissolution and absorption in rats. However, in case of formulations with improved solubility, drug dissolution have a predominant effect on drug absorption rate and concomitant pharmacokinetic behaviour (as reflected in decreased Cmax and AUC values and increased tmax values with prolonged drug release rate).

CONCLUSION: In silico tools offer great potential for the prediction of inhaled drugs pharmacokinetics in both animals and humans, but in order to upgrade these tools, we need to improve our knowledge on animal physiology and correlation between animal and human physiology.

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P9/4

In vitro and in silico aerodynamical evaluation of carrier-free porous inhalable particles

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INTRODUCTION: Dry powder inhalers (DPIs) have been among the fastest developing inhaler types in the past decades. The newest researches report about several high potency carrier-free formulations with low density and optimal aerodynamic properties [1]. Based on this, present work focused on the in silico aerodynamical modelling of the DPI samples of inhalable carrier-free hollow particles prepared with spray drying procedure [2]. We also aimed to test the in vitro aerodynamical stability 1, 10 and 20 weeks after spray drying.

MATERIALS AND METHODS: The active ingredient was the meloxicam (Egis Pcl., Hungary), from which carrier-free porous particles were produced with optimised spray drying procedure using L-leucine, sodium hyaluronate and ammonium carbonate as excipients. Beside the physicochemical properties (size distribution, morphology, density), we determined the in vitro aerodynamics (Andersen Cascade Impactor, 28.3 L/min) and performed in silico modelling of the samples (Stochastic Lung Model applied to COPD patients).

RESULTS: The low density (< 0.20 g/cm3 tap density) carrier-free DPI samples showed the same high aerosolization properties (FPF > 69 %) even weeks after the spray drying (no significant difference). With the in silico modelling we could also determine the exhaled fraction of the particles which was not possible with other methods before.

CONCLUSION: In this research we presented the aerodynamic properties of carrier-free DPI samples, by a combination of methods including the novel in silico assessment for a precise aerodynamical behaviour determination.

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P9/5

Application of a network of artificial neurons on a mixture of powder in a High Shear granulator

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INTRODUCTION: Despite the advancement of knowledge about the granulation of pharmaceutical powders in a high shear granulator (High Shear), there is no theoretical support to date to establish the relationship between the properties of raw materials as well as that the process parameters on the quality of the granules obtained (porosity, dissolution, etc ...).

MATERIALS AND METHODS: The HIGH SHEAR granulator, designed according to the specifications of the DELTA directive, makes it possible to granulate masses of product ranging from 1 to 3 kg. In the case of this study, the granulations are carried out in a 10L stainless steel bowl and on a powder mass of 2 kg, which corresponds to a filling rate of the order of 2/3 usually encountered in industry for a mixer -granulator with high shear.

RESULTS: This work is achieved by the use of artificial neural networks. The results of the model tests showed a strong ability to predict the effects of process variables.

CONCLUSION: This approach can be a pre-

lude to integrating this method into a much broader process called ProcessAnalyticalTechnology (PAT); indeed, the mastery of the quality of the finished products passes by the continuous mastery of the critical parameters of the granulation.

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P9/6

Establishment of requirements for the target measurement uncertainty to validate procedures for the control over the process equipment cleanliness

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INTRODUCTION: The analytical procedures to control the cleanliness of process equipment should be scientifically justified and validated. The uncertainty concept can be used as a scientific basis to assess the quality of analysis results [1]. This work aimed at establishment and verification of requirements for the target measurement uncertainty of analysis results (Ut) with the level of reliability of 95% based on the risk assessment of incorrect decisions on compliance.

MATERIALS AND METHODS: UV-spectrometry, HPLC, titrimetry, oxidisable substances, mathematical statistics.

RESULTS: Having applied normalised coordinates as described in the chapter "5.3.N.2. Validation of analytical procedures and tests" of the State Pharmacopoeia of Ukraine [2], we obtained:

$X(i)=C(i)/C(m)*100$; $Y(i)=r(i)/r(m)*100\%$

where:

C(i) – concentration of the analyte in the test solution; C(m) – maximum acceptable concentration of the analyte (MAC); r(i) – the analytical signal in the test solution; r(m) – the analytical signal of the analyte in the concentration equal to the MAC.

Given that the procedure becomes unreliable if the detection or quantitation limit (DL or QL, respectively) is close to the MAC, we propose to use the following requirements:

DL/MAC>=1/2 (or 50%) – for limit tests;

QL/MAC>=1/3 (or 33%) – for quantitative tests.

According to ICH guidelines, DL and QL are assessed from the results of the linearity study:

DL=3.3S/b; QL=10S/b

where S – standard deviation of the analytical signal; b – the slope of the regression line. This corresponds to the level of reliability of 95%. In normalised coordinates, the expanded uncertainty (U) is:

U=S/b*1.645 (one-tailed confidence interval; 95% reliability level). Combining equations given above, we obtain the following requirements for Ut:

Ut<=16% – for limit tests;

Ut<=5% – for quantitative tests.

Using the set requirements, we performed validation of 23 analytical procedures in the concentration range of residues of APIs from 150 ppm (calcium gluconate, titration) to 0.01 ppm (analgin, spectrometry). The analytical procedures were shown to be fit for their purposes.

CONCLUSION: We established requirements for the target measurement uncertainty for the use in cleaning validation that proved to be feasible and practical.

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P9/7

Risk Assessment based nano-sized liposome formulation development

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INTRODUCTION: Risk Assessment (RA) is the key element of the Quality by Design (QbD) based pharmaceutical developments. The QbD method is a holistic, systemic, science and knowledge focused manner of the pharmaceutical formulation and production process, which is highly recommended by the regulatory authorities [1]. Liposomes offer several potentials in the modern drug delivery. Liposomes in nano-size range can reach new targets and can be applied by alternative administration routes. The conventional formulation

of the liposomes may be replaced by the up-to-date QbD and RA based formulation procedure [2], which is presented by the authors in this study.

MATERIALS AND METHODS: The steps of the QbD and RA based formulation were the following: definition of the quality target product profile, knowledge space development dedicated to the aims, selection of the critical parameters related to the targeted product quality, materials and selected process, performing of the initial RA (QbD LEAN Software®, QbDWorks LLC, USA), design of the experiments based on the RA results, performing the liposome production, liposome product testing (size, size distribution, surface etc.) (Mastersizer S 2000, Malvern Instruments Ltd, UK and Hitachi S-4700 FE-SEM, Hitachi High-Technologies Europe GmbH, Germany) and evaluation of the testing results.

RESULTS: After the proper target determination and cause-and-effect relationship evaluation, the critical parameters were determined and the RA was performed. RA results, like the theoretical ranking of critical factors by their calculated impact score, were presented in Pareto charts and factors with highest estimated impact are presented in the relative severity-relative occurrence diagram. The RA based liposome production was successful, the investigation results showed that the prepared samples fit to the preliminary aimed quality.

CONCLUSION: The QbD approach were used in liposome formulation. The targeted liposome was prepared by a risk-based manner, focused on the most highly risk rated critical elements. Regarding the theoretical screening of the critical factors successful sample preparation by lower experimental effort was reached.

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P9/8

Development of the approach for method transfer for assay of desloratadine in ficoated tablets

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INTRODUCTION: Analytical procedures should be developed taking into account the risk of making incorrect decisions on compliance with specifications [1]. Transfer of analytical procedures (TAP) should be based on the knowledge about the specifics of the object of analysis. The acceptable level of the risk can be assessed using the concept of uncertainty described in chapter „Validation of Analytical Procedures and Tests" of the State Pharmacopoeia of Ukraine (SPhU) [2]. There is a high risk of obtaining inhomogeneous tablet mass when conducting assay in film-coated tablets. Therefore, the development, validation, and transfer of analytical procedures should be carried out using both model solutions and real tablets. This work aimed at developing the metrologically sound TAP for assay of desloratadine.

MATERIALS AND METHODS: A laboratory batch of Alerdez (Borshchahivskiy CPP), film-coated tablets of desloratadine (5 mg per tablet); a procedure for assay of desloratadine validated according to the SPhU approach; an SPhU reference standard of desloratadine (assigned value of 99.7% for spectrophotometry assay); a spectrophotometer Lambda 25, 1-cm cuvette (Perkin Elmer); an analytical balance (Mettler Toledo XP 205DR); a pH-meter (Metrohm); volumetric apparatus ISO Class A were used. An analytical procedure: spectrophotometry, 0.1 M HCl, concentration of desloratadine 0.020 mg/ml (optical density at 282 nm of about 0.64).

RESULTS: The following risks were detected:

a) when validating the procedure using model solutions, the requirements for validation characteristics were met yet the uncertainty associated with the sample weight/dilution taking exceeded that adopted by laboratory practice;

b) when grinding the tablets, acceptable homogeneity was achieved for a sample weight equivalent to 4 tablets. For smaller sample weights, we observed an unacceptably high variation in the assay results.

CONCLUSION: An experiment scheme was developed considering aforementioned risks, and TAP for assay of desloratadine in film-coated tablets with content limits of ±5% was conducted. The procedure relies on the uncertainty concept and metrologically justified criteria, which allows us to control the acceptable level of risk.

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P9/9

Real-time feedback control of continuous pharmaceutical processes using Raman spectrometry and image analysis

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INTRODUCTION: Continuous pharmaceutical manufacturing, both at API production and formulation technology, is rapidly gaining interest as a promising way to improve efficiency, reduce operating costs and ensure easier scale-up and shorter time-to-market. 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 as well as by the big pharma companies. The academia must support these efforts by developing new, innovative continuous technologies, real-time analytics and real-time control strategies to achieve the aimed Process Analytically Controlled Technologies (PACTs). In this work, two feedback controlled continuous manufacturing technologies are presented, first a Raman spectroscopy-based control of continuous powder blending followed by tableting and a real-time image analysis-based control of continuous twin-screw wet granulation (TSWG).

MATERIALS AND METHODS: Continuous blending and TSWG experiments were conducted using multipurpose twin-screw equipment (Quick 2000 Ltd, Tiszavasvári, Hungary). A Kaiser RamanRxn2® Hybrid in situ analyzer (Kaiser Optical Systems, Ann Arbor, USA) coupled with PhAT (Pharmaceutical Area Testing) probe was utilized to acquire the spectra of the homogenized powder and tablets. TSWG was monitored and controlled by real-time imaging and analysis using a process camera and an image analyzer software developed in-house.

RESULTS: The in-line Raman spectroscopic monitoring showed that the applied twin-screw continuous blender was capable of producing blends with high homogeneity and uniform composition. Moreover, 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.

CONSCLUSIONS: The results prove the feasibility of Raman spectroscopy and dynamic image analysis for monitoring and control continuous twin-screw processes such as continuous blending and TSWG.

P9/10

Optimization of freeze-drying process by evaluation the role of time and temperature in lyophilization of biocompatible polymer hydrogels

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INTRODUCTION: Freeze-drying is a technique of drying frozen materials by sublimation of water. Low moisture content, prolonged storage stability, light-weight, porous and hygroscopic solid product can be achieved. Freeze-drying is a time- and energy-intensive process. With the appropriate optimization a lot of time and money can be saved. Higher applied temperature ensures faster freeze-drying cycle, but can cause the damage of the samples. For process development, it is necessary to know the critical properties of the formulation, considering both the drug and the excipients. Glass transition temperature of amorphous materials or eutectic temperature in case of crystalline substances are important to know, because the structure can collapse above this temperature [1]. Freeze-dried biopolymer hydrogel can be produced using alginic salts [2].

MATERIALS AND METHODS: Medium viscosity sodium alginate (Sigma-Aldrich) hydrogels were prepared with purified water swelling on 25°C for 24 hours. The gels were lyophilized in COOLSAFE™ 110-04 freeze dryer (ScanVac, Denmark) at different programs. The moisture content of freeze dried products were evaluated with Karl

Fischer titrator (787KF titrino, Metrohm AG, Switzerland). After reconstitution of dry samples, other investigations were made such as viscosimetry with Kinexus Pro Rheoviscosimeter (Malvern Instr. Ltd, UK) and molecular weight measurements by dynamic light scattering method with Zetasizer Nano ZS (Malvern Instr. Ltd, UK).

RESULTS: The physical and chemical properties of sodium alginate hydrogels depended on the length of freeze-drying cycles included the time of freezing, primary drying and secondary drying. The application of higher temperature ensured a faster drying and a lower moisture content, but the unreasonably high temperature caused the collapse and damage of samples. Viscosity and molecular weight also changed after lyophilization at some cases.

CONCLUSIONS: The length of freeze-drying cycle can be shortened to a limited period of time to achieve a dry product. Applying higher temperature can accelerate drying, but also can cause the damage of the structure.

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P9/11

QSRR modeling of Liquid Chromatography separation of Ziprasidone compounds

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INTRODUCTION: Ziprasidone is an atypical antipsychotic drug with an affinity to the adrenergic (α1), histamine (H1), serotonin (5-HT2), and dopamine (D2) receptors [1]. The first quantitative HPLC analysis of ziprasidone and its five main impurities (I-V) was developed and validated by our research group [2]. The main aims of the presented chemometric study was to develop the QSRR model for the prediction of the chromatographic retention of the other ziprasidone derivatives, or metabolites.

MATERIALS AND METHODS: The minimum energy conformations of the analyzed compounds were obtained by the Molecular Orbital PACkage/Parametric Method Vs.3 (MOPAC/PM3). Molecular descriptors were computed for the optimized molecular models with use of the MarvinSketch 5.1.5.0 program, the Chem3D Ultra 7.0.0 program, CS Gaussian 98 program using the B3LYP hybrid functional. The QSRR study was performed with use of the Soft Independent Modeling of Class Analogy SIMCA P+ 12.0 program [3], for the Partial Least Square (PLS) Regression analysis [4].

RESULTS: The retention times (tR) of ziprasidone and its impurities (obtained with the developed HPLC gradient method) [2], and the computed molecular parameters of the examined compounds were used to build the QSRR models. Descriptors with the highest VIP values were selected for PLS-QSRR model building. Optimal combination of the most relevant descriptors (MS, SAS, LogP, LogDpH 2.5, LogDpH 1.5 and LogDpH 4.0) for PLS models building were chosed on basis of the R2, Q2, RMSEP values of the obtained PLS models. The obtained statistical parameters of the PLS-QSRR model (r2=0.913) pointed out to a good prognostic capacity of the developed QSRR model. The developed PLS-QSRR model was used to predict separation of ten (TS1-TS10) ziprasidone derivatives (organic impurities, metabolites and potential degradation products) in RP-HPLC system. Based on the obtained results, the PLS-QSRR model proposed two structures as potential for unknown impurity (tR: 11.270 min) in the test solution [2], and one of them (TS1) was confirmed by UPLC-MS-MS study.

CONCLUSION: The high agreement between LC-MS results and the QSRR prediction have confirmed good prognostic potential of the created QSRR models. Furthermore, the predicted tR values for TS1-TS10 basically differed from those for ziprasidone and its impurities (I-V) which indicates that the developed QSRR model can be successfully used for the separation of ziprasidone from the other ziprasidone derivatives.

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P9/12

Formulation strategy of anti-microbial peptide (AMP) delivery systems

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INTRODUCTION: Antimicrobial peptides (AMPs) are small and diverse peptides which were initially isolated in the 1980s; Great efforts are done to bring AMPs into therapy with increasing in resistance development to conventional antibiotics. Due to the complexity in stability, safety and efficacy of AMPs, novel formulation strategies, methodologies and delivery systems are required [1, 2].

MATERIALS AND METHODS: As a part of the pre-formulation evaluation of AMP containing dosage forms, SWOT analysis was used to evaluate the formulation possibilities and carrier options, followed by an Ishikawa diagram for illustrating the factors affecting the quality of an AMPs containg drug delivery system. Finally a theoretical initial risk assesment (RA) [3] was made.

RESULTS: Pre-formulation design was performed within the QbD framework. Results of the SWOT analysis showed weaknesses such as low metabolic stability, regulatory barriers and high costs can be defeated by different opportunities which biochemistry and nanotechnology offer for the development of more stable peptides. Besides, threats such as loss of antimicrobial activity and cytotoxicity of AMPs still should be considered and tested. The Ishikawa diagram illustrates all the elements (eg. characteristics of the drug and different methods, etc) which can have an influence on the quality of the AMPs. This diagram was used to select the critical factors, and theoretical initial RA was performed.

CONCLUSION: The pre-formulation evaluation of the AMP containing dosage forms is essential in order to ensure products with the predefined quality.

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P9/13

Data mining of physicochemical, biopharmaceutical and pharmacokinetic properties of model drugs exhibiting low solubility and low permeability

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INTRODUCTION: Data mining is a process of discovering patterns and hidden connections in large data sets by using statistics, artificial intelligence and machine learning tools [1]. The aim of this study was to investigate and identify factors determining drug classification based on diverse set of input data related to physicochemical, biopharmaceutical and pharmacokinetic properties of the selected model drugs exhibiting low solubility and low permeability.

MATERIALS AND METHODS: Database consisting 18 drugs which have been recognized as having solubility and permeability limited absorption (generally classified as BCS class 4 drugs) has been prepared following extensive literature search and critical evaluation of data available. The investigated input parameters were: MW (molecular weight); HB (sum of hydrogen bond donor and acceptor counts); cLogP (calculated partition coefficient); PSA (polar surface area); D/S (dose/solubility ratio); Peff (effective permeability); Fa (fraction drug absorbed); AUC/D (area under the concentration-time curve/dose ratio); Cmax/D (peak plasma concentration/dose ratio); EoM (extent of metabolism), and t1/2 (drug half-life). The analysis has been performed using five parameter combinations: (i) clogP, PSA, HB, MW; (ii) D/S, Fa, Peff; (iia) D/S, Fa, EoM; (iii) Fa, AUC/D, Cmax/D, t1/2; (iv) combination of all the investigated parameters. Hierarchical clustering on principal

components has been employed using Software R, v. 1.1.447.

RESULTS: The number of clusters determined by the software for each combination of input variables ranged from 3 to 6. The following parameters contributed significantly to cluster separation for each of the investigated combinations: (i) clogP and MW; (ii) and (iia) D/S; (iii) AUC/D; (iv) AUC/D and clogP. Although overall match between clusters obtained using different parameter combinations was moderate, it is interesting to note that: a) furosemide, hydrochlorothiazide, chlorothiazide and ciprofloxacin HCl, as well as b) famotidine, cefixime and cefuroxime axetil have been grouped in the same cluster irrespective of the parameter combination used for data analysis.

CONSLUSIONS: Data mining provide useful insight into the similarities between different partitionings leading to recognition of several subgroups within the data set related to model drugs generally classified as BCS class 4.

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P9/14

Wurster Granulation PAT monitoring by NIR: calibration vs PCA trend approach

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INTRODUCTION: One of the main points of investigation to optimize a coating process, is to precisely determine and monitor the process trend.

The aim of this study was the feasibility to apply a NIR device to a fluid bed coating process. Specifically, the possibility to correlate the same NIR response to the moisture content and to the sprayed solution amount.

MATERIALS AND METHODS: In this study, a placebo batch of cores was coated by Wurster coating using fluid bed (FV-VFC Lab3) equipped with a Viavi MicroNIR PAT-U device. Three runs were performed. The process was replicated to demonstrate the robustness of this method. The spectra were collected by the NIR probe every 5 seconds. Data were analyzed and processed by Unscrambler© software.

PCA Analysis: The first data analysis on the spectra collected was the PCA. The PCA locates the combination of directions in this space on which the data are more dispersed, this gives the most quantity of information about the variability of the process parameter during time. The second combination of directions on which the data are most dispersed will be considered the second PCA and it will be perpendicular to the former one and so on. Thus, a new multidimensional space will be defined, having the PCAs as dimensions. This will align every sample on a precise path that allows to follow the process trend during time.

RESULTS: Every deviation can show immediately an anomaly occurred during the process. The interpolation of this graph shows clearly the different phases of the granulation: heating, spraying, drying. Using a NIR device, it is possible to monitor the process using a "trend" approach: observing the changes of the on-line response profile it is possible to analyze the influence of the different process parameters and define the limits of specifications. Furthermore, it is possible to define a calibration curve suitable to be used for the scale-up phase and to keep the production of each batch under control.

CONSLUSIONS: The possibility to follow online the process trend is very valuable to avoid wasting process time, energy and raw materials, and to optimize the process parameters and to obtain a higher quality product.

The process optimization and the possibility to keep it under control is very important for the reproducibility of the final product during time.

This study demonstrated the possibility to follow the process trend.

This could open up the possibility to apply this technology to other techniques, and to implement a full integration of the NIR device with the equipment software to get a complete automatic process control.

P10- PREFORMULATION AND EXCIPIENTS

P10/1

Varrying conditions of in vitro method for assessment of active substances permeability

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INTRODUCTION: In vitro metods have important role in the development of new active substances, as screening methods, but also as supportive metods in biowaiver request submision. They have advantages in these cases in terms of speed, simplicity and lower costs [1]. The possibility of method variation of published dynamic model of diffusion cells with artificial membrane[2] was tested in this study.

MATERIALS AND METHODS: Spectrophotometric assay was validated for determination of concetrations in receptor and donor solution during permeability studies of one representative of active substance from each BCS class: caffeine, naproxen sodium, metformin hydrochloride and hydrochlorothiazide. Apparent permeability coefficients were determined for these substances, with varying support membrane pore size and the origin of lecitine in solution for membrane impregnation (egg and soy lecitines were used) compared to the published method.

RESULTS: Comparison of the obtained results for naproxen sodium with the published results indicate that the pore size of the supportmembrane is not the determining factor for the apparent permeability coeficient. The results of the permeability determinations of the tested substances indicate that the lecitine composition in the solution for impregnation has certain influence. It is determined that the corelation coeficient of the implemented method with the percent in vivo absorption in humans (R2 = 0.9692 for egg lecitine and R2 = 0.9239 for soy lecitine in impregnation solution) is higher than the literature accounts obtained with the other in vitro methods.

CONCLUSION: Based on the examination of varying method conditions of dynamic model of difusion cells with artificial membrane that was carried out, further assessment of method suitability has grounds with the aim of method validation, that could be used for permeability screening purposes of new substances intended to be incorporated in solid oral dosage forms.

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P10/2

Application of PAMPA gastrointestinal model to predict permeability of sumatriptan in free form and in system with cyclodextrin derivatives

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INTRODUCTION: Parallel artificial membrane permeability assay (PAMPA) gastrointestinal model is a method which is used as an in vitro model of passive transcellular permeation for active pharmaceutical substances.

The aim of the present work was to examine the utility of PAMPA gastrointestinal model in predicting permeability of sumatripran and its systems with cyclodextrins.

MATERIALS AND METHODS: Due to low solubility and bioavailability as model drug sumatriptan was chosen. The PAMPA was tested for sumatripran (SUM) as well as its inclusion complexes with β-cyclodextrin (BCD) and hydroxypropyl-β-cyclodextrin (HPBCD).

Permeability studies of sumatriptan and its systems were conducted through artificial membrane using a PAMPA gastrointestinal model at pH 1.2, 4.5 and 6.8. The system consisted of a 96-well microfilter plate and a 96-well filter plate and was divided into two chambers: a donor and an acceptor, separated by a 120-μm-thick microfilter disc coated with a 20% (w/v) dodecane solution of a lecithin mixture (Pion, Inc.). The substances were dissolved in donor solution. The plates were put

together and incubated at 37 °C for 2h. After time plates were separated and the concentrations of substances in donor and acceptor chambers were measured. The apparent permeability coefficients (Papp) were calculated. Compounds with Papp < 1 x 10-6 cm s-1 were classified as low-permeable and those with Papp > 1 x 10-6 cm s-1 as high-permeable compounds.

RESULTS: Sumatriptan showed low values of apparent permeability coefficients under all study conditions. A twofold rise in permeability occurred during the inclusion of SUM into HPBCD (e.g. (0.16±0.01) x 10-6 cm s-1 and (0.40±0.02) x 10-6 cm s-1 at pH 1.2 for SUM and SUM-HPBCD complex, respectively).

CONLUSIONS: Based on the results, PAMPA gastrointestinal model was found as useful tool to compare permeability of sumatriptan in free form and in systems with cyclodextrin derivatives.

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P10/3

Enhanced tedizolid solubility and permeability due to its interactions with hydrophilic biopolymers

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INTRODUCTION: Low solubility of antibiotics is one of the main limitation in their effectiveness. Modification their physicochemical properties in the result of introduction them into binary systems with polymers can be a solution of mentioned limitation. Hydroxypropyl-ß-cyclodextrin (HPBCD) as well as Pluronic® are known as solubilizer agents. While (hydroxypropyl)methylcellulose (HPMC) has been found as prolonge release substance. Increased and prolonged release of antibiotic from pharmaceutical matrix is expected to maintain its constant effective concentration for a longer period of time and thus lead to its more effective absorption.

The aim of the present work was to study the influence of hydrophilic biopolymers (HPBCD, Pluronic, HPMC) on tedizolid dissolution and permeability through artificial membrane of gastrointestinal tract model.

MATERIALS AND METHODS: Tedizolid system with HPBCD was prepared in molar ratios 1:1 while systems with Pluronic® and HPMC in weight ratio 1:1 and 1:5.

In vitro dissolution studies of tedizolid were performed according to European Pharmacopoeia by using an Agilent 708-DS Dissolution Apparatus. As the acceptor solution, 0.1M HCl (pH 1.2) and phosphate buffer (pH 4.5 and 6.8) stimulating gastrointestinal environmental was used. All dissolution profiles were compared with model independent mathematical approach using a similarity factor.

Permeability studies of tedizolid systems were conducted through artificial membrane using a model of parallel artificial membranes permeability assay system (PAMPA). The apparent permeability coefficients (Papp) were calculated.

RESULTS: Dissolution rates of tedizolid were significantly different depending on kind of hydrophilic biopolymers which was used. Furthermore, excipients impacted also on the tedizolid permeability through artificial membranes.

CONLUSIONS: Based on the results, it was found that the presence of hydrophilic biopolymers significantly influence on tedizolid solubility increasing and prolonging its release from the received systems. Modificated release manifests also in extended membrane penetration of tedizolid from its polymeric systems.

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P10/4

In vitro dissolution-absorption study to characterize Itraconazole formulations: The effect of formulation additives, food and dose

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INTRODUCTION: For formulation development traditional (USP) dissolution tests have been used in the pharmaceutical industry to compare performance of different drug formulations before conducting in vivo studies. Although dissolution tests

provide a simple way of testing formulations, the in vivo predictive power of these tests are questionable [1]. When a poorly water-soluble 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. The aim of this study was to represent how simultaneous dissolution-absorption studies can be used for comparing different formulations containing the same API.

MATERIALS AND METHODS: 3 formulations of Itraconazole: Sporanox solution (100 mg), Sporanox capsule (100 mg) and Losanoc capsule (50 mg), were tested using MacroFLUX Receiver chamber integrated with permeation membrane, overhead stirrer and fiber optic UV probe was inserted in the standard 250 mL vessel of USP 2 apparatus. A filter-supported artificial membrane (Double-Sink PAMPA) with 3.69 cm2 area was separating the dissolution compartment from the receiver compartment containing 20 mL of Acceptor Sink Buffer at pH 7.4 (ASB, Pion Inc). Real time concentration monitoring in both dissolution and absorption chambers was enabled through fiber optic UV probes (Pion Inc).

RESULTS: The dissolution and flux results of 3 marketed Itraconazole formulations were compared in fasted and fed state to each other and to the in vivo study results published in the literature. The in vitro test was found to be sensitive enough to show differences between formulations caused by the use of different excipients and rank order the formulations in fasted and fed state as well. The results of the food effect study in case of the Sporanox capsule and the solution are in good agreement with the in vivo data.

CONCLUSION: In contrast with traditional (USP) dissolution tests in case simultaneous dissolution-absorption studies the effect of formulation excipients, dose and food on dissolution and also on membrane transport can be measured. This knowledge is essential for generic formulation development for finding the right additives to be able to meet the bioequivalence criteria.

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P10/5

Solid dispersions of clopidogrel bisulfate: the influence of hydrophilic polymer type on dissolution rate

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INTRODUCTION: Clopidogrel bisulfate (CB) is an anti-platelet drug for the treatment of patients with a high risk of myocardial infarction and belongs to BCS II class drugs. Solid dispersion (SD) is a dispersion of one or more active ingredients in hydrophilic inert carrier matrix and it is one of the most promising and efficient techniques for drug dissolution improvement [1-3].

The aim of this study was to assess the influence of type and concentration of hydrophilic polymer on the CB dissolution rate.

MATERIALS AND METHODS: Four different hydrophilic polymers (Macrogol 6000 (Polyglycol 6000 S), povidone (Kollidon® 30), copovidone (Kollidon® VA 64) and poloxamer 407 (Kolliphor® P 407) and two CB: polymer ratios (1:1 and 1:3) were used to formulate SD using solvent evaporation method, with ethanol as a solvent (96% v/v).

In vitro dissolution testing was performed in USP apparatus 1, with mixing speed 75 rpm, in phosphate buffer pH 6.8, 900 ml, as a medium. All samples contained 75 mg of CB (therapeutic dose). Concentration of CB was determined by HPLC-UV method after 15, 30, 45 and 60 minutes. Dissolution profiles were compared to dissolution profile of CB pure drug.

RESULTS: Results showed that all analyzed SD formulations, except CB:poloxamer 407 (1:1), had better dissolution than the pure CB drug. There was a significant increase in % drug dissolved in SD formulations 1:3 ratios compared to pure CB with the function of time. The obtained results indicated that with the increase in concentration of polymer in formulation, the dissolution rate of drug was increased. This could be due reduction of particle size and an increase in the effective surface area over which the drug distribution increases accompanied by an enhancement in drug dissolution [4].

CONCLUSIONS: Preparation of binary SD with investigated polymers at weight ratio 1:3 significantly enhanced the dissolution rate of the drug compared to pure CB. SD with PEG 6000 and copovidone were the most effective, with concentration of dissolved drug of about 63% after 60 min. This study has shown that the proper selection of type and concentration of hydrophilic polymer played important role in increasing the dissolution rate of CB.

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P10/6

Thermodynamic solubility measurements with minimal consumption of tested substance

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INTRODUCTION: Solubility is a physicochemical property, the determination of which is critical in drug discovery and development as it can affect both technological and biopharmaceutical performance of the drug. Very high throughput and very low compound consumption are realistic with the determination of "kinetic solubility" where the tested compounds are always pre-dissolved in organic solvents like dimethyl sulfoxide [1]. This inevitably results in several imperfections of the obtained data [2]. We have therefore investigated and challenged the limitations of "thermodynamic solubility" measurements by modifications of the traditional shake flask method.

MATERIALS AND METHODS: A simple technique based on the shake-flask method but with minimal use of the tested substance was developed. The thermodynamic solubilities of model compounds verapamil, propranolol, theophylline and digoxin were determined and compared to the available literature data.

RESULTS: The solubility values determined with the novel method agreed well with the previously published solubility data. This agreement includes also the time necessary to reach saturation and the pH dependence of solubility. We have observed that the lowest volume of suspension for the determination of drug solubility does not have to be limited by the efficiency of the mechanical mixing. Medium, but not high throughput is achievable; however, the unavoidable hindrance of true thermodynamic solubility measurements remains the handling of solids.

CONCLUSION: Very low suspension volumes at 50 μL or less can be adequately mixed to provide solubility determination of model compounds in 24 hour experiments. The consumption of the solid substance tested does not have to be higher than 5 mg for a biopharmaceutically valid determination of thermodynamic drug solubility.

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P10/7

Pharmacokinetic properties of fluorescently and PET radiotracer labelled hydroxypropyl-beta-cyclodextrin

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INTRODUCTION: 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 [1]. By the help of fluorescent derivatives the cellular interactions of cyclodextrins can be visualized and their biological activity can be monitored [2]. PET radiotracer labelled derivatives help to understand the in vivo distribution and pharmacokinetics of cyclodextrins. 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. We also aimed to synthetize and test 68Ga-labeled NODAGA-HPBCD.

MATERIALS AND METHODS: FITC-HPBCD

was the product of Cyclolab Ltd, while 68Ga-labeled NODAGA-HPBCD was synthetized at the University of Debrecen. Pharmacokinetic analysis was carried out on BALB/c mice. Small animal PET imaging and ex vivo organ distribution studies were carried out. Cellular internalization was followed by fluorescent microscopy.

RESULTS: The blood concentration of HPBCD 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 techniques 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.

CONCLUSION: The in vivo behaviour of fluorescent cyclodextrins can be examined by fluorescent and PET 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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P10/8

Biocompatibility investigation of pharmaceutical excipients

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ABSTRACT: Introduction: Preservatives are substances that are added to the product to prevent it from spoilage. They act by inhibiting specific enzymes of the bacteria or inhibiting the growth of the bacteria. Nowadays we can experience increased attention from the consumers towards the safety of different pharmaceutical excipients such as preservatives. There are more and more complaints reported by patients of irritation that may be related to the the preservative content of the formulations. This is why it's important to test their biocompatibility and see whether they are harmful or not.

MATERIALS AND METHODS: We tested three of the most commonly used groups of preservatives: parabens, sorbates and salicylates. All preservatives were dissolved in PBS. The solutions of the paranbens contained other excipients as well to better simulate real pharmaceutical formulations. To test for the cytotoxic effect we used MTT assay and RT-CES assay. MTT assay is based on the mithochondrial activity of viable cells. The cells convert the MTT paint to formazan precipitate. RT-CES assay is based on measuring the electrical impedance in the presence of the tested compound. This way we can get information of the cell growth rate. The experiments were executed on Caco-2 cells. The Caco-2 cell line is great to model the gastrointestinal tract.

RESULTS: The cytotoxicity of the methyl paraben is changing, depending on what other excipients we used in the solutions. Both MTT assay and RT-CES results confirm that. In the case of sorbates according to the MTT assay results there is no difference between the cytotoxicity of the salts. According to the RT-CES results only potassium sorbate is safe to use and sodium sorbate seems to be toxic to human cells.

CONCLUSIONS: The cytotoxicity depends on the composition, there is no general cytotoxicity value that can describe a compound, it needs to be checked every time when a new pharmaceutical drug is formulated.

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P10/9

Study on the effect of multivalent cations and matrix formers applied for microencapsulation

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INTRODUCTION: Ionotropic gelation occurring as a consequence of chemical reaction between ionic gel-forming polymer solutions and counter ions is a possible method for the production of drug-loaded microcapsules. Several factors play significant role in the course of coacervation: temperature, ion concentration, polymer concentration, pH. The observation that the crosslinking ion concentration of the coacervation medium influences gelation is published in the case of gelatin, agarose, pectin, alginate. The most examined relation is Ca^{2+}- alginate in complex coacervation [1, 2].

In our experiments the phenomenon was studied in the presence of various di-/trivalent cations to observe the role of type and concentration of the ions on the gelation and phase separation.

MATERIALS AND METHODS: Different gel-forming polymers were investigated, among these the most examined sodium alginate along with Ca^{2+}, Mg^{2+}, Fe^{2+}, Fe^{3+}, Al^{3+} and Bi^{3+} ions to determine the optimal parameters for coacervation. Potentiometric titration (Hanna HI902C Automatic Potentiometric Titration System, Hanna Instruments, USA) aided the specification of the most proper parameters of phase separation. The optimal conditions were applied to form microspheres with Büchi B-390 Microencapsulator (Büchi GmbH, Switzerland) using vibrating nozzle technique. The morphological parameter testing was carried out using laser diffractometry (Malvern Instruments, Malvern, UK), scanning electron microscopy (Hitachi 2360 N Hitachi Ltd., Tokyo, Japan) microscopic image analysis (Nikon SMZ 1000 and ImageJ Software) to define the particle size distribution and shape determination of the produced beads.

RESULTS: Our investigations proved the different ability of cations in the formation of stable, spherical beads with alginate, which may offer the opportunity to choose the most convenient excipients and parameters in the microencapsulation of active ingredients related to drug release.

CONCLUSION: The experiments provide source for the development of a stable m: icroencapsulated drug-carrier system.

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P10/10

Complexation of chrysin by β-cyclodextrin derivatives and their biological activities

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INTRODUCTION: Chrysin is a poorly soluble bioflavonoid with several biological effect and can be found in several plant extract including also propolis and honey. It has anti-inflammatory, antioxidant and anticancer activity [1, 2]. Our aim was to test the chrysin solubilisation capacity of different β-cyclodextrin derivatives and prepare complexes to examine their biological activity, especially on the NF-κB pathway.

MATERIALS AND METHODS: Cyclodextrins were the product of Cyclolab Ltd, all other reagents were from Sigma-Aldrich. Chrysin-cyclodextrin complexes were produced by liophylisation in different molar ratios. Phase-solubility test was performed with β-, (BCD) Hydroxypropyl-β-, (HPBCD) Sulfobutylether-β-, (SBEBCD) and Randomly-methylated-β-cyclodextrin (RAMEB) and the concentration of dissolved chrysin was determined by HPLC method. Cytotoxicity of the complexes was tested by MTT test and the inhibition of NF-κB pathway activation was investigated by immunofluorescence, labelling the p65 subunit.

RESULTS: Phase-solubility experiments showed, that each cyclodextrin increased the solubility of chrysin, but there were significant differences among the derivatives. SBEBCD, RAMEB and HPBCD were able to effectively solubilize chrysin, while BCD showed limited capacity. MTT test revealed that up to 100 μM concentration the

examined complexes were not cytotoxic on Caco-2 cells. Investigating the NF-κB inflammatory pathway we found, that the pre-treatment of Caco-2 cells with chrysin-cyclodextrin complexes decreased the TNF-α-induced nuclear translocation of p65.

CONCLUSION: In conclusion, cyclodextrin derivatives are able to effectively improve the water solubility of chrysin and the formed complexes are not cytotoxic in the tested concentration range. The complexes are able to inhibit the main inflammatory pathway, NF-κB and cyclodextrins had no negative influence on the effect.

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P10/11

Does particle size distribution influence solid fat content of potential novel drug carriers?

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INTRODUCTION: One of the crucial factors in patients' compliance with orally taken medicine is definitely the drug taste. As many active pharmaceutical ingredients exhibit an unpleasant taste, taste-masking becomes particularly important [1]. On the other hand, the taste of chocolate has become one of the most popular flavors throughout the world. The main fat type used in chocolate production is cocoa butter. However, in order to reduce costs and implement new functionalities to confectionery systems, various vegetable fats and oils are being used as cocoa butter replacement. So, this may potentially make a cheap alternative carrier for drugs with an unpleasant taste.

But in order to achieve a quality confectionery product, one of the most important factors to follow and measure is its solid fat content (SFC) [2]. The aim of this work was to measure the impact of particle size distribution of sugar and/or cocoa particles on SFC of vegetable oil, as this mixture may make a potential drug carrier for drugs with unpleasant taste.

MATERIALS AND METHODS: Different blends were prepared by using palm oil and sugar and cocoa particles of different sizes. SFC measurements were conducted by pulsed NMR on a Bruker Minispec SFC analyzer by direct method (AOCS (Cd 16-b-93)). The liquid mixtures of oil with sugar, cocoa, and sugar and cocoa were transferred into pNMR tubes, cooled in a water bath from 65 °C to 20 °C at a rate of 0.5 °C/min and then left in a temperature cabinet at 20 °C for 7 days. Before analysis, pNMR tubes with samples were heated to 65 °C for 30 min. The analyses were conducted in triplicates for each sample.

RESULTS: Results of the pNMR measurements showed that the only significant difference in SFC occurred in samples containing only sugar. Among these samples, those with smaller particles had higher solid fat content. Samples containing only cocoa or sugar and cocoa particles did not show significant difference in SFC due to different particle size distribution.

CONCLUSION: Since particle addition had only minor or no effect on the SFC, this matrix may present a good starting point for the inclusion of a thermostable active pharmaceutical ingredient, in order to create an attractive drug dosage form with the taste-masking ability.

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P10/12

Photostability of hydrophilic vitamins

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INTRODUCTION: Hydrophilic vitamins are essential nutrients, which, in case of inadequate intake or increased requirements, should be added as supplements. Multivitamin products are available in solid and liquid dosage forms for enteral and parenteral administration. Due to vitamins reactive nature, stability issues arise, which are more evident in dissolved state. Hydrophilic vitamins are generally light-sensitive, though, more detailed and systematic data on their photostability is not available in the literature [1].

MATERIALS AND METHODS: Hydrophilic vitamins in forms, most commonly present in pharmaceuticals were tested: vitamin C, B1, B2, B3, B5, B6, B7, B9 and B12.

Vitamins were determined according to a validated stability-indicating method using Agilent UHPLC Infinity 1290 instrument with a DAD detector. Chromatographic separation was performed on a XSelect CSH C18 column (150 × 4.6 mm, 3.5 μm) with a gradient elution mode consisting of 25 mM NaH_2PO_4 and MeOH.

Photostability testing was performed in a Memmert ICH 260 L climate chamber in accordance with ICH Q1B guidelines [2] and was consisted of two parts: forced degradation and confirmatory testing of each vitamin`s aqueous solution. Confirmatory testing was additionally performed on various vitamin combinations in different concentrations (in proportions such as in multivitamin products).

RESULTS: Forced degradation study revealed that hydrophilic vitamins are generally light-sensitive. Vitamin B2 and B9 were found most susceptible to photodegradation. Vitamins photostability was found temperature and pH dependent. Their photostability was also evaluated in various combinations to reveal interactions and possible incompatibilities. Most of them were found more stable in presence of other vitamins. The stabilization effect was most often due to vitamin C. However, some vitamins, such as vitamin B9 and B12 were more prone to photodegradation when in combination with others, especially with vitamin B2.

CONCLUSIONS: Overall, hydrophilic vitamins (individually or in combinations) were found light-sensitive. The obtained results offer valuable information regarding vitamins stability in parenteral nutrition admixtures.

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P10/13

Combining mechanochemistry and spray congealing towards new praziquantel formulations

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INTRODUCTION: Praziquantel (PZQ) is the first line drug used in endemic countries for the treatment of schistosome infections and is included in the WHO Model List of Essential Medicines for Children. Several approaches have been undertaken to reduce the high PZQ therapeutic dose thanks to its solubility enhancement. Among them, some strategies involving the drug mechanochemical activation (MA) provided improved biopharmaceutical properties, thanks to different crystal modifications of PZQ [1, 2]. In this study, the association of MA and the spray congealing (SC) technology was evaluated for developing a child-friendly PZQ dosage form with better product handling and Praziquantel biopharmaceutical properties compared to MA materials.

MATERIALS AND METHODS: To obtain (PZQ) Form B, having improved solubility and bioactivity [2], PZQ was neat ground in a Retsch MM400 vibrational mill. in addition, A 1:1 PZQ: Povidone coground was prepared in the same vibrational mill under cryogenic conditions, for favouring amorphysation upon milling [1]. Then, microparticles, using the self-emulsifying agent

Gelucire® 50/13 as carrier, were produced by the SC technology. Both the activated powders and the corresponding loaded microparticles were characterized for morphology, wettability, solubility, dissolution behaviour, drug content and drug solid state (HSM, DSC, PXRD and FT-IR). Finally, samples were in vitro tested in comparison to PZQ against S. mansoni newly transformed schistosomula (NTS) and adults.

RESULTS: As a consequence of incorporation in the self-emulsifying agent by SC, the MPs containing both MA systems showed a further increase of biopharmaceutical properties compared to the milled powders. The in vitro antischistosomal activity showed that MPs enabled PZQ release, while maintaining its bioactivity.

CONCLUSIONS: The microparticles containing PZQ Form B are a promising product for designing a new PZQ formulation.

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P10/14

Micellisation of Binary Mixture of Surfactants Sodium-Deoxycholate and Sodium-Decyl Sulfate in Water Solution: Thermodynamic Description

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INTRODUCTION: This paper covers experimental determination of the critical micelle concentration (cmc) of the mixed micelles of Sodium-Deoxycholate (NaDC) and Sodium-Decyl Sulfate (SC10), as well as the calculation of the parameters which describe thermodynamic stability of the examined mixed micelles.

MATERIAL AND METHODS: The solutions of NaDC and SC10 were used to produce mixtures of surfactants, in various molar ratios. Critical micelle concentrations of the obtained mixed micelles were determined by using spectrofluorometric analysis, on the following temperatures: 10, 25, 35 and 50 °C [1,2].

RESULTS: Experimentally obtained cmc values of binary micelles were lower than ideal cmc values calculated for the respective binary mixtures, which proves the existence of interactions between NaDC and SC10 in the real mixed micelles. Negative values of the interaction parameter and the excess Gibbs energy (calculated by Regular Solution Theory) were obtained at all the examined temperatures. These results confirm the existence of attractive interactions between the different components of the mixed micelle. Values of the excess Gibbs energy calculated by Rodenas´s model independent method were negative for most examined mixed micelles. Testing the symmetry of the function, which represents dependence of excess Gibbs energy on mole fraction of the more hydrophobic surfactant in the mixed micelles, showed the necessity of using two-parametric functions.

CONCLUSION: The occurrence of synergism in mixed micelles of NaDC and SC10 most probably is the consequence of the thermodynamic stabilisation of micelles, due to the creation of hydrogen bonds among sulphate groups of SC10 and hydroxyl groups of NaDC.

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P11- REGULATORY AFFAIRS

P11/1

Fighting against Falsified Pharmaceuticals by 2D Laser Coding Technology in Case of Using Naturally Colored Polymer Film Coating

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INTRODUCTION: Substandard and/or falsified medicines are a growing global threat for health and they cause serious social and economic damage. According to the new reports from WHO (2017), in the low- and middle-income countries

the failure rate of substandard and falsified medical products is approximately 10.5% [1, 2]. Medicines purchased over the Internet could be fake in 50% [3, 4].

The current project is focusing on the development of a technology to mark an individual traceable 2D code directly on the surface of the tablet to make it easier to differentiate between fake and genuine drugs. As the demand for natural materials is growing, the research was extended to naturally colored polymer films, too. Usually coatings contain titanium dioxide and talc for sufficient coverage, which makes precision laser coding more difficult. New natural films, the subjects of our examination, do not include the excipients mentioned above. In this research we would like to make a comparison of physical-chemical properties after the laser marking procedure between the conventional and natural colored coatings.

MATERIALS AND METHODS: HPMC coating polymers: Sepifilm PW Red, Green, White and Sepifilm Naturally Colored Pink and Green (Seppic S.A.) were marked by ArF excimer pulse laser and semiconductor laser. After marking polymer films, analytical quality control was made by Raman spectroscopy, thermal gravimetric analysis and scanning electron microscope.

RESULTS: Structural change was seen by Raman spectroscopy both in conventional and natural polymer films treated with the semiconductor laser, while the excimer laser did not cause significant alteration in the films. Thermogravimetry showed no significant result for the different films. The pre- and post-laser structure was examined by SEM as well.

CONSLUSION: This study examined how conventional coating materials behave compared to coatings with natural paint during laser marking. The results demonstrated that marking tablets by excimer laser could be the right instrument for naturally and conventionally colored coating polymers, too.

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P11/2

Transport and biotransformation of gliclazide in probiotic bacteria

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INTRODUCTION: Gliclazide is a drug characterized by large interindividual differences in therapeutic response. However, the cause of these differences is not fully explained. It is known that interindividual differences in gut microflora composition may affect drug metabolism and therapeutic response (1). Thus, the aim of the present study was to investigate the transport and biotransformation of gliclazide in probiotic bacteria in in vitro conditions.

MATERIALS AND METHODS: Samples of gliclazide with probiotics were incubated for 24 hours at 37 °C. The intracellular and extracellular concentrations of gliclazide were determined in seven time points by high-performance liquid chromatography. Gliclazide biotransformation by enzymatic activity of probiotic bacteria was predicted by appropriate software packages.

RESULTS: During the twenty-four-hour incubation with probiotic bacteria, in all time points, statistically significantly lower concentrations of gliclazide in extracellular content were observed compared to controls. In addition, the total content of gliclazide, as a sum of intracellular and extracellular concentrations, was statistically significantly lower compared to control throughout the whole studied period. Proposed metabolic pathways of gliclazide biotransformation by the action of probiotic bacteria involve reactions of hydrolysis and hydroxylation.

CONCLUSION: Based on the obtained results, it can be concluded that part of gliclazide is transported into probiotic bacteria, while part of drug is metabolized by the activity of bacterial enzymes. Interactions of gliclazide with probiotic bacteria at intestinal level might be the cause of interindividual variations in drug response that is still to be confirmed in in vivo conditions.

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P11/3

Non-toxic bile acids as pharmaceutical excipients may alter pharmacological activity of antitumor drug vorinostat

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INTRODUCTION: The unique structure and physicochemical properties of bile acids have enabled them to be used in the development of drugs, as excipients and drug carriers that could improve, control and localize drug delivery [1]. Hydrophobicity is the main determinant of bile acids toxicity and depends on the number, position and orientation of the hydroxyl groups. Replacement of hydroxyl groups by keto groups in the structure of bile acids makes them more hydrophilic and less toxic and thus suitable for the use as drug excipients [2]. We aimed to analyze the impact of non-toxic bile acids, the most hydrophilic natural bile acid ursodeoxycholic acid (UDCA) and semi-synthetic 12-monoketocholic acid (MKC) on pharmacological (cytotoxic) activity of antitumor drug vorinostat against colon cells.

MATERIALS AND METHODS: Human colon adenocarcinoma HT-29 cells were used to assess the cytotoxicity of vorinostat, alone or in combination with bile acids UDCA and MKC, using the colorimetric MTT assay. Multiple drug effects were examined by calculating the combination index (CI) using CompuSyn software. CI1 is evidence of antagonism.

RESULTS: Vorinostat exhibited a modest cytotoxic activity (IC50 = 5.1 μM), while UDCA and MKC were shown to be non-toxic against HT-29 cells (IC50 352 μM and 212 μM, respectively). The co-incubation of cells with clinically relevant concentrations of vorinostat (1 μM and 2 μM) and non-toxic (IC20) concentrations of UDCA (50 μM) and MKC (35 μM) over 48h resulted in significant increase of cytotoxicity. Calculated CIs of 0.05 and 0.04 for UDCA, in combination with 1 μM and 2 μM vorinostat respectively, demonstrated that UDCA exerted strong synergistic activity with vorinostat in concentrations that can be achieved in vivo. MKC also managed to sensitize cells towards activity of vorinostat, with more pronounced effect in a combination with 2 μM vorinostat (CI = 0.04) than in a lower concentration (CI = 0.10).

CONCLUSIONS: Response to vorinostat may be altered by combining it with bile acids as drug excipients. The mechanisms responsible for this synergistic effect should be more in-depth investigated.

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P11/4

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

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INTRODUCTION: 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.

MATERIALS AND METHODS: Our aim was

to compare the cellular internalization of fluorescein and rhodamine labeled hydroxypropyl (HPBCD) and randomly-methylated beta-cyclodextrins (RAMEB). Using fluorescent microscopy and flow cytometry we tested the endocytosis of the fluorescent cyclodextrins on Caco-2 cells. We also examined the effect of these cyclodextrins on Nf-kappa B pathway and autophagy on Caco-2 cells.

RESULTS: Both fluorescein and rhodamine labeled 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 quantitative analysis.

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P11/5

Liraglutide 3.0 mg for weight loss, Is it more effective in diabetic or non-diabetic patients? A systematic review and meta-analysis

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INTRODUCTION: Liraglutide is an analogue of Glucagon-Like Peptide-1 (GLP-1) which was approved for treatment of type 2 diabetes mellitus at doses of 1.2 and 1.8 after that was approved at dose of 3.0 mg for treatment of obesity in combination with diet and exercise. Efficacy of liraglutide for weight loss was studied for diabetic and non-diabetic patients as well. The objective of this review is to determine if liraglutide is more effective in diabetic versus non diabetic patients.

MATERIALS AND METHODS: We conducted a systematic review and meta-analysis of randomized clinical trials (RCT) comparing Efficacy of liraglutide 3.0 mg for weight loss among diabetic and non-diabetic patients. We searched PubMed, Ovid Medline, Google Scholar and Cochrane Library databases relevant published studies in English from March 2008 until March 2018. We estimated standard Mean difference (Std. MD) with 95% confidence intervals using random effects model and assessed for heterogeneity (I2).

RESULTS: We screened a total of 42 studies related to liraglutide efficacy for weight loss from which four studies (with 4678 patients) studies met our inclusion criteria. One of them studied liraglutide efficacy in weight loss in diabetic patients, while the other three studied liraglutide efficacy in weight loss in non-diabetic patients. Weight loss in non-diabetic patients was statistically higher (Std. MD 0.80 CI 0.74 to 0.86, P= 0.49 I2 = 0%)

This meta-analysis of RCTs showed that weight loss due to liraglutide use in non-diabetic patients was statistically higher than it in diabetic patients.

OTHER: More trials on diabetic patients using liraglutide for weight loss are required. Also more trials on variant ethnicities are required.

P11/6

Preference and adherence to once – monthly versus once weekly bisphosphonates in patients with osteoporosis: a systematic review and meta-analysis

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INTRODUCTION: Once-weekly and once-monthly bisphosphonates are considered revolutionary dosing intervals for osteoporosis. Many patients with osteoporosis went through both dosing intervals but still not clear which dosing interval is most favorable for patients. The objective of this study was to determine whether Once-weekly or once-monthly is more satisfied and results in more drug adherence.

MATERIALS AND METHODS: We conducted

a systematic review and meta-analysis of randomized clinical trials (RCT) comparing patients preference and drug adherence for monthly dosed bisphosphonates (Ibandronate and minodrenate) versus weekly dosed bisphosphonates (resideronates and alendronate). We searched PubMed, Ovid Medline, Google Scholar and Cochrane Library databases relevant published studies in English until March 2018. We estimated Preference differences with 95% confidence intervals using random effects model and assessed for heterogeneity (I2).

RESULTS: We screened a total of 23 studies related to bisphosphonates dosing interval from which four (with 1004 patients) studies met our inclusion criteria. Two studies used alendronate, while one used residronates and one used both alendronate and resideronates as weekly bisphosphonates. For monthly bisphosphonates, three studies used Ibandronate, while one used Minodroate. In comparison with either once-monthly or once-weekly. Preference for once-monthly bisphosphonates was statistically higher, the pooled preference was (0.43, 95% CI 0.39 to 0.47, P = 0.61, I2 = 0%). Also adherence to once-monthly bisphosphonates was statistically higher (0.38, 95% CI 0.34 to 0.42, P = 0.52, I2 = 0%).

This meta-analysis of RCTs showed that once-monthly bisphosphonates dose interval use was associated with higher patient preference and therapy adherence compared to once-weekly for adults with osteoporosis.

OTHER: Studies conducted on White and Asian women. There is lack of researches on other women ethnicities also on men with osteoporosis.

P11/7

Implementation of Patient Reported Outcome Measures (PROMs) in QbD based formulation development in opthalmology

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INTRODUCTION: PROMs are important to both the clinician and the researcher, and they may be used to assess health-related quality of life, or to assess symptoms or perception of health status. The development of most PROMs in ophthalmic research has been driven by the recognition that clinical tests (visual acuity, perimetry, ocular coherence tomography), imperfectly capture the extent to which patients are impacted by sight impairment [1]. Beside this, there can be other systemic, psychological, emotional and social effects of both the disease and its treatment [2].

The aim of this "Quality by Design" (QbD) based study is to extend the usage of PROMs to the early R& D phase, together with physicians' expectations and researchers' perspectives as well.

MATERIALS AND METHODS: Evaluation of scientific literature, guidelines and regulations concerning the parameters affecting patients' quality of life; an adaptation of the extended QbD model is proposed for the development of ophthalmic preparations [3].

RESULTS: The research team developed a new model for QbD based formulation design process in case of ophthalmic dosage forms. Patients' perceptions were collected by means of generalized and disease specific questionnaires; followed by gathering information from the health care providers about the product performance. Based on these evaluations an optimized formulation design can be achieved in order to have in an improved therapeutic efficiency and patient adherence. A prior strategic planning according to the QbD framework and its adaptation to a special therapeutic area e.g. ophthalmology is an advanced manner to have a patient user friendly product on the market.

CONCLUSION: The model can be a useful tool in the selection of the dosage form and the critical quality attributes from patients' point of view.

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P11/8

Pharmacokinetic-pharmacodynamic model of sedation with fentanyl in critically ill children who are mechanically ventilated

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INTRODUCTION: Fentanyl dosing in children is complex, as pharmacokinetic (PK) and pharmacodynamic (PD) parameters differ significantly from adults and also among pediatric population. We aimed to develop a PK-PD model of sedation with fentanyl in mechanically ventilated critically ill children.

MATERIALS AND METHODS: We included 49 children (less than 2 years) with severe acute bronchiolitis, who were mechanically ventilated and received intravenous infusion of fentanyl for at least 3 days. During the infusion 5 blood samples were taken. Sedation and anaesthesia were monitored by COMFORT-B scale and bispectral index (BIS). COMT Val158Met, ABCB1 C3435T and OPRM1 A118G genetic polymorphisms were determined. Population PK model of fentanyl was developed using NONMEM software. Sequential PK-PD model of sedation was developed by modelling the relationship with COMFORT-B score and BIS.

RESULTS: The final pk model of fentanyl was a two compartment model with the estimated volume of central compartment 109 L/70 kg, volume of peripheral compartment 39.9 L/70 kg, clearance 36.6 L/h/70 kg, and distribution clearance 87.1 L/h/70 kg. The clearance was influenced by bodyweight and postmenstrual age (PMA). The later reflects maturation of clearance independently from the effect of body weight, which was included in the model by allometric scaling. We estimated that clearance achieves 50% of the adult value in a full-term newborn aged 3.5 weeks.

PK-PD relationship with COMFORT-B and BIS were adequately described by a sigmoidal Emax model. The tolerance was modelled as an interaction with partial agonist accumulated in a hypothetical tolerance compartment. In the model for COMFORT-B COMT genotype influenced intrinsic potency of fentanyl, which was almost 80% higher in carriers of variant allele compared to homozygous wild-type. In the model for BIS efficacy of fentanyl was 14.8% higher in patients with ABCB1 variant homozygote genotype. PMA influenced intrinsic potency and efficacy of fentanyl. Consequently, in older children higher doses of fentanyl were required to achieve the same level of sedation.

CONCLUSION: In the developed PK-PD models bodyweight, PMA, COMT and ABCB1 gene polymorphisms influenced the levels of sedation achieved by continuous infusion of fentanyl in critically ill children who were mechanically ventilated. The model enables individualization of fentanyl dosing in the studied population.

P11/9

ATP Bioluminescence for surface contamination control in hospital pharmacy premises

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INTRODUCTION: In order to control the quality of hospital pharmacy clean rooms we implemented a new alternative and rapid bioluminescence method for measuring the overall ATP, and indirectly bioburden of surfaces in the hospital environments [1]. We assumed that despite the low microbial load of tested environment the method is sufficiently sensitive for routine use and, due to simplicity useful as a quick and effective tool for quality control and a tool for detecting change and monitoring trends [2, 3].

MATERIALS AND METHODS: The testing was performed parallel to routine microbiological control. Firstly we divided our premises into several meaningful categories, defined the action limits, and then searched for the correlation of methods by individual categories. The basic principle of bioluminescence method is enzyme-catalysed reaction in the presence of ATP. The technique includes the sample collection, the implementation of the enzyme reaction and the detection of during reaction released light by using a lab luminometer Kikkoman (Lumitester PD 30). The obtained results were evaluated for relevance and the methods were compared with respect to performance in finding an inadequate surface (chi-squared test).

RESULTS: In places with more stringent requirements we did not confirm any significant differences between compared methods ($p=1$), while the new method is more sensitive in places with less stringent requirements ($p<0.05$).

CONCLUSION: The used method measures the overall ATP from living cells and ATP released from dead cells or residues of used materials. It represents an important approach where quick accessibility of the results is needed and which provides possibility to implement corrective measures immediately.

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P11/10

Use of Antidepressants in Republic of Serbia from 2013 to 2015

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INTRODUCTION: Depression is a chronic mental disorder that causes changes in mood, thoughts, behavior and physical health. According to the World Health Organization (WHO) 350 million people worldwide are said to suffer from this mental disorder. This explains why antidepressants are widely used [1, 2]. The aim of this study was to analyze the use of antidepressants in Serbia, Norway and Finland from 2013 to 2015.

MATERIAL AND METHODS: The data about the use of antidepressants in Serbia, Norway and Finland in 2013, 2014 and 2015 was taken from the Agency for Drugs and Medical Devices of the Republic of Serbia, the sites of Norwegian Institute of Public Health, and Finish Agency for Drugs Fimea.

RESULTS: Large number of depressed patients and smaller number of antidepressants used in Serbia compared to Finland and Norway in 2013, 2014 and 2015 can be explained by a different socioeconomic status and different health system in those three countries. Patients in Serbia are underdiagnosed and undertreated due to a failure of the primary care physicians to identify depressed patients, so that those can be treated by a psychiatrist at the secondary health care level. Sertralin is the first-choice medication in Serbia compared to escitalopram in Norway and Finland. Escitalopram has the highest probability of remission of the investigated antidepressants and is the most effective and cost-effective pharmacological treatment strategy for depression in a primary care setting.

CONCLUSION: The consumption of antidepressants in Serbia increased in 2015 compared to 2013, but was still significantly less in Serbia in 2013, 2014 and 2015 compared to Finland and Norway, pharmacotherapeutically developed countries. Medications consumed the most in all 3 countries in 2013, 2014 and 2015 were selective serotonin reuptake inhibitors. Sertraline was the most widely used antidepressant in Serbia in 2015, while escitalopram was mostly used antidepressant in Norway and Finland.

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Use of Hypolipidemic Drugs in Serbia in The Period 2013 to 2015

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INTRODUCTION: Cardiovascular diseases (CVD) are the leading cause of dying in the world. One of the groups for the treatment of CVD are hypolipidemic drugs [1]. The aim of this study was to analyze the consumption of hypolipidemic drugs in Serbia in the period from 2013 to 2015, and to compare this data with Norway and Finland.

MATERIALS AND METHODS: The data about the use of drugs are taken from the official web site from the Agency for Medicines and Medical Devices Agency of Serbia, Norwegian Insti-

tute of Public Health and Agency for Drugs of Finland.

RESULTS: In Serbia, the use of hypolipidemic drugs is small and the drugs occupy a 4-5 % of all drugs in the treatment of CVD. In Norway and Finland consumption of hypolipidemic drugs is much more bigger, and among all drugs in the treatment of CVD the consumption of hypolipidemic drugs is on the second place during that period (Norway 30% and Finland 20% of all drugs in the treatment of CVD). Among all hypolipidemic drugs, the most used drugs are statins, and among statins the most used drugs are simvastatin and atorvastatin in all three investigated countries. In Serbia on first place in 2013/2014/2015 is atorvastatin (11.68/9.47/20.98 DDD), and on second place in 2013/2014/2015 is simvastatin (3.67/3.53/3.36 DDD). In Norway on first place in 2013/2014/2015 is atorvastatin (58.10/62.85/70.43 DDD), and on second place in 2013/2014/2015 is simvastatin (50.77/47.22/43.17 DDD). In Finland on first place in 2013/2014/2015 is simvastatin (46.87/43.80/44.43 DDD), and on second place in 2013/2014/2015 is atorvastatin (27.52/31.72/36.65 DDD).

CONCLUSION: In observed period it is noticeable trend of increased consumption of statins in all three countries. We also notice that Serbia is the country with the lowest consumption of this drugs.

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