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A jövő kötelez

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1924 – 2020

Debrecen, 2020. szeptember 10-12.

Congressus Pharmaceuticus Hungaricus XVI.

Debrecen, 2020. szeptember 10–12.

Abstracts

Established in 1925. by Pál Lipták

A **Teva** a világ legnagyobb generikus gyógyszergyártója, mely több mint **100 éves tapasztalatával** fejleszti, gyártja és értékesíti termékeit. Portfoliójába - a generikus gyógyszerek mellett - számos originális termék, vény nélkül kapható gyógyszer, élelmiszer kiegészítő és gyógyászati segédeszköz is tartozik. Termékeivel több mint 60 országban van jelen.

Magyarországon a Teva több mint 25 éve van jelen. **Debreceni** és **sajóbábonyi üzemében a kutatás-fejlesztési** tevékenységtől az **alapanyag-gyártáson** keresztül a **kész gyógyszergyártásig** és törzskönyvezésig számos tevékenység folyik. A magyarországi gyártóüzemeiből európai, amerikai és más nemzetközi piacokra is exportál.

A Teva a hazai gyógyszerpiac egyik vezető vállalata, mely **2019-ben a legtöbb doboz gyógyszert forgalmazta** Magyarországon.* A Teva elkötelezett a minőség iránt, magas minőségű termékei betegek százezreinek jelentenek javulást, gyógyulást és tesznek lehetővé jobb életminőséget.

Forrás: *IQVIA: 2019 sell-in dobozforgalom

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PLENARY LECTURES

ISTVÁN ANTAL, FULL PROFESSOR
Department of Pharmaceutics, Semmelweis University, Budapest

Pharmaceutical technological innovations serving therapeutical safety and efficacy

Background: There is a growing interest toward the development of innovative pharmaceutical dosage forms that provide new opportunities for improving the safety and efficacy of drug therapy. The innovatively structured and functioning formulation based on advanced excipients may serve as a drug delivery system capable of increasing efficacy and / or reducing side effects through innovative technological solutions. The active ingredient is an essential component of pharmaceutical formulations, but the dosage form is the one which carries and liberates its contents as drug substance targeted to the site of action. Various polymeric excipients and manufacturing processes can be used for formulations and their structures allow to modulate drug release mechanisms and to optimize the pharmacokinetic profiles.
Aims: The objective of the review is to present the new results of the development of pharmaceutical technology related to marketed medicinal products, as well as to the latest literature and own research and developmental data.
Methods: Aspects of presentation and evaluation: patient compliance and therapeutic adherence, conditions and special warning of use, pharmacokinetic profile, appropriate bioavailability, desired onset and duration of action, improved dosage regimen, manufacturability and quality.
Results: Many novel formulations have gained therapeutic and diagnostic significance. Depending on the mode of application, they may be incorporated into solid (capsules, tablets, sachets), semi-solid (gels, creams, pastes) or liquid (solutions, suspensions, or parenteral) dosage forms. Nanoparticles (e.g., nanocrystals, vesicles, conjugates) are useful not only for solubilization but also for reducing side effects through targeted drug delivery. The microparticles increase applicability and, as independent drug delivery units, result in predictable and predictable blood levels. Digital pharmaceutical technology represents a new development trend, combining formulation and information technology solutions for tracking as well as to enable treatment management, collaboration and therapeutic adherence.
Conclusions: It has become clear that the right dosage form is an important prerequisite for the success of therapy, and that patient-centricity, personalized and precision medicine requires a paradigm shift in the field of pharmaceutical technology.

References: 1 Stegemann, S., et al. Eur J Pharm Sci 2011;44(4):447-454; 2 Lengyel M. et al. Sci Pharm 2019;87:1-31.

LAJOS BOTZ, FULL PROFESSOR
Department of Pharmaceutics and Central Clinical Pharmacy, University of Pécs, Pécs

Utilization of real world data to evaluate and optimize drug therapy

With the rapid growth of data-driven healthcare and digital medicine real world data (RWD) are increasingly used to improve drug therapy and clinical research. The utilization of RWD offers both physicians and practicing pharmacists the opportunity to improve drug therapy and engage in drug development. Thereby healthcare patient care can deliver "data driven" in both research and routine care.
We aimed to explore the potential of domestic RWD through some practical issues related to medication and therapeutic outcomes.
The data required for our studies were obtained from the available health care databases in Hungary (PULVITA, NHIFH or NEAK, IQVIA) and from the clinical database of Clinical Center of University of Pécs. The period analyzed, depending on the individual issues, was between 2000 and 2018. The collected data covered the entire process and history of individual patient care.

We aimed to address four major questions. First we investigated high-risk drug combinations. Based on data of prescription collection of four years, it could be stated that the problem we are facing is far from negligible, as incidence of the riskiest drug pairs (ca 40) is approximately 1.8 million per year. Our second investigation focused on adverse drug reactions. We wanted to find out whether the Hungarian hospital database can be used for such purposes besides the known sources of ADRs. It was found that the number of cases that could be determined by more than a hundred ICD codes was high, which proved the novel applicability of RWD. The presented third study of medications of schizophrenic patients was based on the use of active substances and outcomes. It especially focused on rehospitalization events, based on hospital and outpatient care data between 2010-2016. The fourth study shows aimed to determine relationships between the nutritional status of patients and their clinical data, to evaulate whether malnutrition can affect the output of healing. The observed data-patterns confirmed, that consequential effect of malnutrition can concern up to 20-50% of patients (depending on the disease).

Our studies demonstrate that RWD analysis can be useful for improving therapy, despite its many limitations. Comprehensive understanding of RWD collection and analysis is needed to achieve its full potential. This way, drug development can become continuous and involve both practicing physicians and pharmacists.

ISTVÁN GREINER, RESEARCH DIRECTOR
Gedeon Richter Plc., Budapest

New chemical entity R&D at a CEE midpharma company (From here to eternity)

As the cost of new chemical and/or biological entity R&D is continuously increasing, reaching 1.5-2.5 billion USD, its feasibility in case of a midpharma company is getting to be more and more questionable. At the same time it is even more challenging in the CEE environment where both the financial and the human resources are much more limited than in the developed countries. Notwithstanding the aforesaid four years ago a compound invented and co-developed in Hungary has got marketing authorization in the US, the biggest market of pharma products on the world. The success is ongoing, now its sales reached nearly half billion last year and can jump up to 1 billion USD peak sales according some analysts. During my lecture a short story of cariprazine R&D and in connection with it the related challenges we are facing here will be presented. While I have no crystal ball to show the future only my ideas and thoughts will be shared with the participants about the possible way out from this labyrinth and reach success on this very difficult field of innovation.

BALÁZS HANKÓ, DEPUTY STATE SECRETARY FOR HIGHER EDUCATION
Ministry of Innovation and Technology, Budapest

Society and Health Policy Aspects of the XXI. Century Education of Pharmacists

Significant changes in the healthcare system in recent times have also transformed the expectations of pharmacists, mainly in the areas of community and hospital pharmacy and, of course, the pharmaceutical industry. Thus, the regulatory environment of the pharmacy system has been completely changed, which has extended the duties and responsibilities of pharmacists. The pharmaceutical industry, as a priority sector of the national economy, further strengthened. The R & D & I of the pharmaceutical-related health industry is also evolving significantly. Renewed pharmacy education must be able to reflect all these changes in both the graduate and postgraduate fields and within the functional structure of Faculty. It also requires the development of a university infrastructure environment. The main directions of change are as follows:

- *Increasing the proportion of pharmaceutical subjects under the curriculum,*
- *Development of teaching-related infrastructure,*
- *Increase the involvement of practitioners in education and strengthen pharmacy and industrial practice training,*
- *Development of the functional structure of the Faculty of Pharmacy, integrated education in clinics,*
- *Faculty developments must be in line with the national health and pharmaceutical strategic objective,*
- *Expanding domestic and international courses in the Faculties of Pharmacy.*

ZOLTÁN SZILVÁSSY, RECTOR, FULL PROFESSOR
University of Debrecen, Debrecen

Innovation trilemma (Higher education and Industry cooperation)

Aim: My work is referred to as an approach to the phenomenon of 'globalisation paradoxone'through potential role of universities with special regards to pharmaceutical industry.
Basic concept and methods: We think that the key element in building an effective pharmainnovation system is a stable cooperation among pharmaceutical companies and a multidisciplinary knowledge centres the latter of which represented by universities and/or academic research institutions. The optimum form of cooperation at least according to our experiences is the creation of industrial clusters of in which the universities serve as knowledge centres with significant capacities of both multilevel education and experimental and clinical research. Moreover, these baseline university medical research capabilities if supplemented with a wide range of natural sciences such as physics, chemistry, biology and informatics and sciences of law end economics within an institution may render the knowledge centre a highly competitive centre of competence.
Results: One and a half decade ago, the University of Debrecen was successful in building an university-industry network in pharmaceutical industry with Richter Gedeon pharmaceutical company as a principal player together with numerous small and SMEs, a system strongly supported by the local government termed Pharmapolis Innovative Cluster of Pharmaceutical Industry. This 'triple helix' innovation structure was then supplemented with participation of financial institutions succeding generation of distinct projects entering the clinical phase. Phase 2/1 results were found to attract either financial partners or capable of eliciting an interest from global players outside the cluster. It is a point of importance that the cluster members are at least in part owned by Hungarian share holders. The major results of the development of the system beyond producing competitive products and/or product candidates derive from creation of manufacturing plants in the city belonging to either directly to pharmaceutical industry or presenting as externals of the particular industrial branch such as manufacturing and distributing radiodiagnostics or offices dealing with regulatory affairs. These results together may answer questions of the major economic trilemma of modern societies as to whether strenghtening of national self-definition, globalisation and/or democratic economy policy is of preference.
Conclusion: We conclude education and university-based innovation of high quality in structured collaboration with national companies yield very good conditions for globalisation.

MÁTYÁS SZENTIVÁNYI, DIRECTOR GENERAL
National Institute of Pharmacy and Nutrition

How does OGYÉI help the Hungarian pharmaceutical industry?

New era in the pharmaceutical industry is just here. National Competent Authorities like OGYÉI are acting as real authorities and are approving, inspecting, etc. this field. On the other hand, however, OGYÉI is acting as a supporter of the industry and cooperates with the different stakeholders. We provide scientific advises, and try to help the industry in different ways to cope with new regulations. Besides this we do everything we can to keep the stability of the Hungarian pharma market. We work in close collaboration with our stakeholders and we make decisions after consulting with them or we help them to understand new regulations. OGYÉI follows the different laws and regulations and has its own priorities but always wants to make life of the stakeholders easier and wants to ensure that the decisions made are realistic and will result in the processes they are aimed for. OGYÉI is committed to help new innovation and to help those who need support e.g. small and mid-size companies. We always work on updating our financial support program to make financial support happen, too. We are confident that with these actions we will ensure that the Hungarian pharma industry can continue to work as well as its history is determining it.

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PRE-CONGRESS LECTURES: SERIALIZATION

Assessment of the Hungarian serialisation status after one year – what is behind us and what is still to come

ANTAL FELLER
Hungaroharma Ltd.

As a result of the closed distribution channels, the strict regulatory environment and cooperation between the participants no counterfeit medicines have entered distribution via pharmacies (retail and institutional) in Hungary. In the interest of being able to comply with the EU Directive that entered into force on 9 February 2019, and for the above statement to remain true in the future too, all pharmaceutical production and distribution participants have complied with the prescriptions of the Directive. The founders established the HUMVO Magyarországi Gyógyszer-azonosítási Nonprofit Zártkörűen Működő Részvénytársaság [HUMVO Hungarian Pharmaceutical Identification Nonprofit Closed Stock Company], HUMVO set up the HUMVS system, the pharmaceuticals manufacturers have applied unique identifiers to their prescription products and have created tamper evident packaging, have uploaded / are uploading the product identifiers to the European database, the end users have joined the system, and are continuously performing identification and reporting. All this has represented a very serious financial burden for all market participants. After a year, within the stabilisation period, we can now say that we have caught up, and within the EU we are in fourth or fifth place in terms of operation (proportion of those joining the system, absolute number of controls and reports, and the most important indicator, the ratio of false alarms). What is still to come? The system is operational, and we are now in the fine-tuning phase:

- We have to set up an alarm mechanism that, after the expiry of the stabilisation period, takes us to the point of certainty in suspicious cases (the product is certainly not a counterfeit, i.e. it may be released / it is very probably a counterfeit product, i.e. it may not be released);
- Hungarian legislation gave exemption from joining the system for certain products and end users until 9 February 2021 – it is necessary to decide what to do after this deadline expires...

And all this must be implemented so that drug safety is not violated in Hungary, and so that there is no reduction in confidence in the supply of medicines, in other words all patients are able to obtain safe therapy at the appropriate time and place using the medicinal product prescribed for them.

Implementation of EU Falsified Medicines Directive in the Hungarian hospitals

ANDRÁS FITTLER[1], KATALIN RICHTER[2]
[1]*Department of Pharmaceutics, University of Pécs, Pécs;*
[2]*Hospital of Szent Borbála, Tatabánya*

The EU falsified Medicines Directive 2011/62/EU delegated regulation came into force and has been applied in Hungary since 9th of February 2019. Implementation of the directive in community pharmacies was in the focus of attention, however it was somewhat unclear how decommissioning would be managed within hospitals and how hospital pharmacists will deal with the upcoming tasks. Based on interviews with practicing hospital pharmacists, literature review and our representative online questionnaire amongst Hungarian hospital pharmacies the supply chain from the retailer to the pharmacy, and the drug commissioning and distribution process within the hospital to wards are discussed in the presentation. Furthermore, due to the relative lack of in-depth assessments of cost implications for hospital pharmacies, we describe the financial burden of FMD on Hungarian hospitals based on human resource requirements, infrastructural and IT developments and authentication procedures. The FMD has notable short and long term impact on hospital pharmacies. Identification and dissemination of good practices in serialization during the stabilization period, and the discussion of potential forthcoming opportunities (e.g. stock management, automation solutions) will likely support hospital pharmacy practice.

The greatest challenges for the pharmaceutical industry: serialization_

LÍVIA ILKU,
Gedeon Richter Plc.

According to European law; pharmaceutical products must comply with the requirements of serialization according to Directive 2011/62/EU (FMD) of the European Parliament and of the Council of 8th June, 2011 amending Directive 2001/83/EC of the Community code relating to medicinal products for human use, in regards to the prevention of the en-

try into the legal supply chain of falsified medicinal products and its related Commission Delegated Regulation (EU) 2016/161 (Delegated Regulation). Products released after 9th of February, 2019 must comply with the above regulations and with the relevant specific regulations in the market where the product is intended to be sold. The aim is to establish appropriate processes that increase transparency and facilitate an audit trail, while at the same time being in full compliance with GDP and FMD requirements. One of the greatest challenges for the pharmaceutical industry over the past year has been understanding the rules of serialisation and make them operational. Prior to February 9, 2019, we focused on the corporate level to understand the requirements, as Marketing Authorization Holder to structure the data, create the system and upload the information to repositories. As manufacturer ensure that new safety features are placed on the boxes and as Wholesaler perform verifications, decommissions and undo-decommissions in the National Medicines Verification System ("NMVS"). Pharmaceutical companies, including Richter, supported the project with enormous financial and human resources. After February 9, 2019, the system was launched, the main task was maintaining the process. We are currently in a stabilization period, meaning that alerts issued by the system, although generating a task for the supply chain, can be dispensed to the patient for most of the alerts. At the same time, several authorities have indicated that they will to close the stabilization period as soon as possible and, accordingly, they have set expectations for the alert process. Alert handling is of paramount importance because, at the end of the stabilization period, counterfeiting-related alert preparations cannot be dispensed to patients. This can lead to patient care problems. So the issue of proper alert management and closure of the stabilization period is a key concern for all participants in the supply chain. The task of regulation must therefore be addressed with a view toward ensuring the safe and secure supply chain of medicines to patients.

Obligations and experiences of the national competent authority after the first year of the pharmaceutical serialization

ÁDÁM PANKER
National Institute of Pharmacy and Nutrition

The pharmaceutical serialization is a relatively new approach to help secure pharmaceutical products around the world but it is already expected to cover approximately 80% of the global drug supply. It was not surprising that the European Union also decided to apply this strategy because as the European Parliament and the Council stated in the Directive 2011/62/EU, "there is an alarming increase of medicinal products detected in the Union which were falsified in relation to their identity, history or source", and "such falsified medicinal products do not reach patients only through illegal means, but via the legal supply chain as well". The pharmaceutical serialization was expected to stop this unfavourable phenomenon but in some member states like Hungary where the supply chain was safe traditionally, it is debated if initial costs exceed benefits. Although the European Commission declared that all stakeholders must be ready to meet their obligations on 9th February 2019, it was predictable that for such complex and varied supply system like the European the available time will be not enough to complete all these tasks. This resulted in an awkward situation for national competent authorities, whose responsibility was to supervise the functioning of the new end-to-end verification system and sanction any violations without causing any drug shortages at the same time. Because of the above, OGYÉI proclaimed a stabilization period and tried to play an active role as facilitator to help all stakeholders to comply. Over the past year, many problems had to be solved which were sometimes unpredictable. Many batches generated false alerts making hard to filter out potentially real falsification cases and it revealed the need for an alert handling protocol. By now, also the authority and the industry gathered enough experience to make the next step in ending the stabilization period.

ORAL PRESENTATION

Pharmaceutical activities of the former Hungarian order province of hospitaller order of St John of God

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Background: The Hospitaller Order of St John of God was founded by Juan Ciudad in 1537 in Granada, Spain. Their first place of working in the Central European region was Feldsberg/Valtice, where a convent was established in 1605. On the territory of the Hungarian Kingdom the order members settled in the second half of 17th century. The Hungarian Order Province was established in 1856 and its existence suspended after 2nd Word War. Up to 1918, the Province included 13 convents, each of them operated a hospital and pharmacy.
Aims: To characterize the main attributes of everyday operation of the pharmacies run by the Order, with special attention to their location, equipment, assortment and personnel.
Methods: Methods of historical research were applied to reconstruct the past pharmaceutical activities of the Order. As main sources were used archival documents and other historical sources published in the studied period (journals, statistical publications, order schematisms, etc.).
Results: Historical sources from the studied period make possible the reconstruction of several partial attributes of pharmacy operation. Based on the study of authentic archival documents were obtained valuable data on the furniture and equipment of the pharmacies, logistics and economic aspects of their operation, contacts of the pharmacies with other specialized workplaces, like hospitals, pharmaceutical manufacturers, wholesalers or educational institutions.
Conclusion: The Hospitaller Order of St John of God played an important role in the development of modern healthcare and pharmacy culture and forming of the network of healthcare facilities. Historical research oriented to the study of Order's pharmaceutical activities gives specific information related to the healthcare services provided by religious orders, and could also contribute to generalization of the knowledge of historical development of pharmacy network.

Formulation and stability testing of inhalable powder preparation containing an antibiotic agent

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Background: Pulmonary drug delivery can be divided into three main categories (pressured metered-dose inhalers, nebulizers and dry powder inhalers /DPIs/). Recently, the development of DPI products observed due to the production of traditional, carrier-based and carrier-free DPI systems. It should be emphasized that the harmony of the DPI formulation, the DPI device, and the patient are essential to achieve successful inhalation performance. Because most DPI devices are capsule-based, after the phase of particle engineering the investigation of DPI capsules has become more important to have the final dosage form [1, 2].
Aims: Our recent work introduced a novel combined formulation method, where the surface modification of the inhaled lactose and particle engineering of the drug were used before the blending. Therefore, the effect of magnesium stearate and sodium stearate on the final formulation was investigated. The effect of different DPI capsule types (gelatine, gelatine-PEG, HPMC) on the stability of novel combined formulated DPI samples was tested.
Methods: Ciprofloxacin (CIP) was the applied model drug. The developed novel formulation was filled in different capsules and stored (6 months) according to ICH guidelines. As a physical examination, particle size distribution, morphology and structure were studied. The in vitro aerosolization properties were investigated with the Andersen Cascade Impactor.
Results: The same formulation was filled in different capsules showed almost consistent lung deposition results before storage, but after 1, 3 and 6 months, the formulation stored in the HPMC capsule clearly had the best aerodynamic values, which correlated with the results of physical examinations. It can be established that the properties of the capsule shells influence the aerosolization results due to the change in the residual water content of the capsules, in the size and shape of the punctured area, and the different morphology of the DPI powder.
Conclusion: The development of dry powder inhalation capsules by manufacturers and the testing of

DPI powders in different capsules open a new way to increase the effectiveness of DPI products.
Acknowledgment: EFOP-3.6.2-16-2017-00006 LIVE LONGER project is acknowledged.

References: 1 Wauthoz, N. et al., Int. J. Pharm., 2018;553:47-56; 2 Ambrus, R. et al., Eur. J. Pharm. Sci. 2018;123:20-27

Heritable and environmental factors in schizophrenia and depression

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Common disorders are called also complex disorders that are characterized by heritable and environmental factors. The ratio of heritable and environmental factors is, however, highly variable. This is true also for psychiatric disorders. Ratio of heritable factors is high (> 80%) in schizophrenia and bipolar disorder (formerly bipolar depression), and low (ca. 30-40%) in major depression (unipolar depression). Heritable factors were calculated in twin studies earlier, but genomics took it over with the development of genotyping technology in genome wide association studies (GWASs), where the ratio of millions of genetic variants are compared in case (disorder) and control (healthy) populations without any information about environmental factors. Highly significant effects of several variants have been described in schizophrenia and bipolar disorder in GWAS studies providing evidence for the significance of heritable factors. Furthermore, there is a relatively broad overlap in the presense of these variants in these two disorders. In major depression, however, the number of reproducible hits is very low. In conclusion, genomic studies suggest that there are similarities in the biological background of schizophrenia and bipolar disorder, while ethiopathology of major depression is different.

Chromone derivatives as modulators of oxidative stress: in vitro biological evaluation and oxidative transformation

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Background: Oxidative stress (OS) is a phenomenon, which is related to the formation of free radicals and reactive oxygen species in excess. One of the major consequences of OS is the damage of biological macromolecules leading to the development and/or progression of numerous illnesses. Nowadays, there is an increase in the application of natural products for the prevention of different disorders, or adjuvant substances next to pharmacological treatment. Phytochemicals include different chromone derivatives, which possess a wide spectrum of biological activity.
Aims: In the present study we investigated the antioxidant activity, cytotoxicity and oxidative transformation of ten chromone derivatives.
Methods: We determined the radical scavenging activity (ABTS, DPPH, Galvinoxyl), the oxygen radical absorption capacity (ORAC) and the ferric reducing antioxidant power (FRAP) of the tested molecules. The cytotoxicity and their effects against H_2O_2 induced cell death were studied on H9c2 cell cultures by MTT assay. Finally, we investigated the oxidative transformation of the molecules. The oxidation was carried out by Fenton-reaction and the potential metabolites were detected by LC-MS/MS.
Results: The molecules have negligible effect against Galvinoxyl and DPPH radicals, while compound 2243 and 1675 showed significant activity against ABTS. In case of FRAP assay 2243 and 1675 also possessed significant effect, however, molecule No. 1617 exhibited the highest FRAP value. Furthermore, compound 2243 has low ORAC value, while 1675 and 1617 were the most active compounds during the ORAC assay. Based on the MTT assay neither of the molecules showed cytotoxicity. Moreover, those molecules, which showed significant activity in the antioxidant assays (1617, 1675, 2243), significantly improved the cell viability, when the cells were treated with H_2O_2 compared with the positive control.
Conclusion: In conclusion, based on the results the (2E)-3-(4-oxo-4H-chromen-3-yl)prop-2-enoic acid (1617), 4-oxo-4H-chromen-3-carboxilyc acid (1675) and 3-[5-(chloromethyl)-1,3,4-oxadiazol-2-yl]-4H-chromen-4-on (2243) possess significant antioxidant activity, non-cytotoxic at the applied concentration and stable metabolically, hence, it is worth to investigate further in OS related diseases models.

Acknowledgement: This study was supported by the GINOP-2.3.2-15-2016-00043 (IRONHEART), the Higher Education Institutional Excellence Program NKFIH-1150-6/2019 and EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" projects.

Novel investigation methods and innovative 3D printing possibilities in the pharmaceutical technology

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Background: Nowadays, 3D printing is one of the major top 10 innovative research fields in the pharmaceutical sciences. Rapid prototyping and additive

manufacturing are also the synonimes of this technique. Briefly, it is a layer by layer printing process using special digital code. The first step is the design which could be computer aided design or 2D method where the structures of layers are planned. The second step is the conversion of these design for STL file, which is mainly the basis of 3D printing. In the third step, the raw materials are prepared as granules, extruded filament or binding solutions. Finally, as the last step the product is printed layer by layer, then solidification and the removing of supplementary components are made. 3D printing techniques have many benefits, because complex, personalized products are manufactured by automated, low-cost operation. 3D printing is widely used in the field of arts, architecture, industry, nevertheless it has a great impact on the preparation of medical, pharmaceutical products.

Aims: The presentation objective is to give a short summary about the methods which have high application possibility in the pharmacy and pharmaceutical industry.

Methods: In this review, inkjet printing, stereolithography, fused filament fabrication method, hot melt extrusion technology are summarized.

Results: In the pharmaceutical industry, Spritam was the first FDA approved medicine in 2015, it was produced by ZipDose technology. Thin powder layer was bound, it was repated until the appropriate tablet format was reached.

Conclusion: The main pharmaceutical significance of 3D printing is the rapid, individualized, personalized medication, however qualification and authorisation of the printed products have to be regulated.

References: 1 Alhnan, M. AT. et al., Pharmaceut Res 2016;33:1817-1832; 2 Liska, R, et al., J. Coat Tech Res 2007;4:505-510

Challenges for the next quarter century. Quality in hospital pharmacy – hospital pharmaceutical quality development framework

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In the last quarter of the 20th century, the supply of medicines has been steadily improving, and the reliability of supply has increased. In the recent past, development has come to a halt and shortcomings are beginning to emerge again. Pharmacy must be prepared for the challenges of the next quarter of this century.

What are the most important factors in changing the economy and society and how should pharmacists prepare for it?

Negative trends, dangers are as follows:
- *economic crises*
- *climate crisis*
- *increase in energy and logistics costs*
- *an aging society*
- *decrease in active money earners*
- *more expensive research*
- *mental illnesses, abuses*
- *outbreaks of epidemics*

Positive trends, opportunities:
- *Industry 4.0*
- *Society 5.0*
- *digital world, artificial intelligence, big data*
- *development of education*

All members of the pharmaceutical profession must be prepared for the changes. Together with economic and state actors, pharmaceutical and professional organizations are developing programs for change. In addition to securing financial resources, the task is to reduce losses and make better use of opportunities and opportunities. Applying positive trends to practice will be key to development.

The quality requirements of the hospital pharmacy fit tight to the function of the health care provider institution. The quality of the medication determines basically the efficiency of the therapy. Hospital pharmacists must closely cooperate with other health care personnel. In the international practice there are preconceived standards for the cooperation between hospital pharmacists and associate professions. Therefore, we can access both to the European (EAHP) and American (ASHP) hospital pharmaceutical standards.

Our aim was to create the quality management frame of the hospital pharmacy after summarizing the standards concerning Hungarian hospital pharmacy.

We have processed the standards of Hungarian health care system regarding to pharmacy. We have also processed the ASHP (American Society of Health-System Pharmacists) Guidelines: Minimal Standards for Pharmacies in Hospitals, and the standards of the European Association of Hospital Pharmacists (EAHP).

We have formulated the quality management requirements of hospital pharmacy. The Hungarian Society of Hospital Pharmacists have published it in a book form.

The publication is necessary for hospital pharmacists. It is practical to provide a training for all hospi-

tal pharmacists in order to introduce them the standards.
Reference: Becskeházi-Tar A, et al.: Minőség a kórházi gyógyszerészetben; Klinikai Gyógyszerészeti Minőségfejlesztési Keretrendszer; Galenus Kiadó Budapest, 2019. ISBN 978-963-7157-56-1

The implementing and evaluating of Medication Management standards in cases Joint Commission Accreditation and Hungarian Health Care Standards (MEES)

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Background: As hospital pharmacists have expanded their role from simple drug dispensing to patient-oriented clinical practice, they have augmented their professionalism (the attitude sand belief as professional and quality) as hospital pharmacists. This it has been important to make them commit to hospital quality standardization and evaluation programmes based on several international or national standard frameworks. Introducing and evaluating standards is a big challenge for pharmacists because: – they do not have sufficient experience in audit, – no professional network of evaluators yet, – there are several standards that contradict the Hungarian rules – for example the use of own medications. The management of personal medical treatmentsof patients hospitalised in health facilities follows regulatory requirements. Failure to respect these requirements may resultin iatrogenesis, with sometimes severe consequences for thepatients.
Aims: My goal is to present my own audit experience gained over the past 12 years in implementing and evaluating of Medication Management standards in cases Joint Comission Accreditation and Hungarian Health Care Standards (MEES). I have a special focus: The detection of critical errors and opportunities for improvement in cases of patients' own medications.
Methods: Audit has been realised in order toassess how the medical staff follow standard criterias, riskmatrix and protocols on medical data sheets and personal awareness.
Results: Of the 379 audit reports submitted about patients taking their own medications from home while in the hospital, more than 25% of the reports mention a medication considered to be a "high-alert" medication. High-alert medications are medications that have an increased risk of causing significant patient harm when they are used in error. The reports also showed that nearly 8% of the reported events resulted in a transfer of the patient to a higher level of care, with 67% of these cases involving patients taking their own controlled substances (narcotic/pain meds) from home.
Conclusion: Let's give space for common answers – interactive quiz: Why Do Patients Bring Their Own Medications? What Do Clinical Pharmacist Need to Know to for Patients safety? How do prepare for an audit? What role do risk assessments and problem-solving techniques play in evaluation? What competencies are needed in the audit team? How to multiplicate auditor knowledge?

New perspectives of skin penetration investigational methods for dermal preparations

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Background: Dermal drug therapy has increasing importance nowadays in drug development. Modelling of penetration into the skin is a complex challenge. Human skin tests give the most relevant information however, because of the high cost, it is advisable to choose simpler methods in the early stages of development of dermal preparations. Not only the device, the membrane and acceptor solution, but also the properties of the carrier system itself influence how the particular system can be most effectively tested.
Aims: The aim of this work was to summarize the novel knowledge about the main in vitro methods available to study the skin penetration and present various experimental models used to investigate drug penetration into the skin effectively.
Methods: There are many types of equipment on which in vitro release tests (IVRT) and in vitro permeation tests (IVPT) of drug carrier systems can be performed. Two types of vertical Franz diffusion cell (Hanson Microette TM Topical & Transdermal Diffusion Cell System and LOGAN Automated Dry heat sampling system) with different membranes (synthetic and biological) and the Skin-PAMPA method have been compared.
Results: The reproducibility, sensitivity and specificity of the method are essential for reliable in vitro testing. Based on our results, we can select the optimal in vitro test for modelling the penetration into human skin, and in vivo results can be predicted.
Conclusion: In this work, the most well-known and state-of-the-art methods for studying drug penetration through the skin have been presented, which can provide significant support during the development phase of the dermal preparations.

How to plan a smart patient safety sytem?

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Background: Smart devices are gaining more and more ground in our everyday lives. Robots and virtual assistants are popping up left and right. Until today, however, the Hungarian health care system has been resisting the spread of modern technology, partly due to the peculiarities of the financing system and the passive resistance of professionals.
Aims: By utilizing innovative technologies of the private sector and by taking the special needs of the healthcare institution into account, our goal is to create an IT system that records the data in a central database in a form that can be analyzed by decision support algorithms, and thus support medical decisions according to the expectations of the 21st century. In addition, the medical system should be able to manage and automatically document medication, nursing, and medical activities performed according to protocols.
Method: In a development project financed by a tender, we are carrying out a transformation on our medical system with the help of the participating system administrator, which makes it possible to record the patient documentation data as described above. To plan the transformation of the medical system, we set up a multidisciplinary working group, which included delegates from the IT company, our own IT specialists, clinicians from various professional groups and pharmacists.
Results: After months of consultation, the working group prepared a detailed specification of the database and a feasibility study. The programmers handed over a beta version of the modified program. Testing of the program has been started by members of the planning committee and will be continued by the pilot departments once the identified errors have been corrected. Integration into the daily patient care routine is a time-consuming process, but we plan to extend certain functions to the entire institution within a year.
Conclusion: Based on our experience so far, we have concluded that the construction of such a complex system is only possible with the involvement of dedicated professionals. One of the most important participants in the working group is the mediator, who can translate between healthcare professionals and IT professionals. The reason for failure in most of these attempts is that the developer and the customer do not understand each other..

New medication-related developments in The Hungarian Electronic Prescription System and other eHealth services

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In all countries, where electronic health services such as e-prescriptions have been introduced, patient safety has improved and the standard of medical and pharmaceutical care has increased. ePrescription (eRecept) - launched in Hungary as well - has become the most used eHealth module of the EESZT (National eHealth Infrastructure) by all healthcare providers in the past near 3 years. During the COVID epidemic emergency e-prescription system has been a huge help to patients, relatives and caregivers too. In this period the proportion of electronic issued prescriptions exceeded 90% of all prescriptions written.
The e-prescription system contributes to the better and faster information of healthcare professionals, supports the well-based therapy decisions, helps preventing and eliminating medication errors. Adverse drug reactions (allergies, interactions, polypharmacy etc.) can be more easily identified with the daily use of this service. Less paper administration can increase the time and quality of patient counseling both at the doctor's and in the pharmacies. Medication adherence can also be simply monitored by pharmacist as well. After patient registration - using social security number (SSN/ TAJ) -, written maximum 1 year earlier and/ or by other pharmacy dispensed prescriptions will be also downloadable soon from the central database. These functions and real time data contribute to the implementation of high-quality pharmacotherapy advising services in pharmacies as healthcare institutions, made in accordance with the specific standards and protocols.
The new functions of the Patient Portal (e.g. Legal Representation) and mobile surfaces provide patients and their relatives access to follow their care process, prescriptions, labs, etc., already on their smartphone too. From the beginning of May 2020, serial-produced medical aids mostly sold in pharmacies, can be electronically issued. The full integration of all the medical aids may be completed next year in a separated module. A simple web-based prescriber (so-called miniHIS) has been developed for connected private doctors, who do not consult in institutions.
Measured values of the (smart) medical devices can be uploaded into the personal data repository of the

Patient Portal on a voluntary basis. Good measurement results of the blood pressure, sugar, body weight, etc. recorded here demonstrate therapy fidelity, providing feedback to the patient and professionals. Telemonitoring services can be build on this module, so the software can send alerts to the assigned doctor, pharmacist or family member.
Keeping data protection rules strict, depersonalized pharmacotherapy data uploaded to the central eHealth database will be searchable soon for professional and scientific purposes.

A break in the drug supply chain

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Background: What does medication shortage mean? As a practicing pharmacist, we have a different concept behind than OGYÉI, or even a pharmaceutical manufacturer. Neither will the patient or the customer be more reassured if we provide the official legal explanation for the seemingly simple question, "Why don't I get my medicine?"
Aims: What is the important for us in the community pharmacies, is whether we can provide the patient with a solution? As the last link in the chain, we are also a collision interface, as this presents us a toll on our everyday practice. Sometimes we know the answer, sometimes we have little information about why we can't make the desired order for the patient. What's really going on in the background may be unknown for many colleagues working in community pharmacies…
Methods: Where does the story medicine shortage start? I searched through the supply chain for possible causes, development and resolution of medicine shortages: starting from the authorities and pharmaceutical manufacturers, wholesalers, raw material manufacturers, and finishing at the pharmacy.
Results: Officially reported reasons for shortage in case of registered pharmaceuticals may be shipping, storage problems, active ingredient, raw material issues, manufacturing issues, market considerations, increased market demand, administrative issues, etc. The real reason usually can be described by a complex set of factors. Since officially only registered products are considered for shortage, I dealt with them only during my analysis, guiding them through the market. According to the possibilities of the development of the drug shortage, I found different reasons among the market players. There are specific deficiencies specific per each particular actor.
Conclusion: What reflects the views of all actors involved in supply chain management are shortage of labour, the rise in quality standards, the globally expanding market, which has led to over-demand rather than over-supply.

An overview of health management patterns: preferences, adherence and the electronic prescription attitudes in the community pharmacy

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Background: Health self-management of pharmacy customers has a complex impact on society beyond individual well-being, and our priority is to know and improve the determinants thereof, such as preferences, adherence, and to describe and use attitudes related to the electronic prescription, all of which serve the purpose of compiling a better community pharmacy service package for patients.
Aims: In the cross-sectional, retrospective study, our goal is to assess, on a representative sample of n = 472 people, what the elements of patient health management are, what are their main characteristics, and what conclusion can be drawn for a community pharmacy.
Methods: We created our own Hungarian questionnaire consisting of 20 questions for the survey. We have sought to use language that is understandable to the patient, and to create simple and quick questions that require no more than 10 minutes to complete.
Results: The results describe the profiles, preferences, attitudes of patients of two pharmacies in Budapest and the Department of Ophthalmology, as well as the current status of electronic prescription as an increasingly popular and frequent service. The current study is being developed to a longitudinal one, which provides further insights into the community pharmacy aspects of the above questions.
Conclusion: There are different trends across ages of patients regarding pharmacy loyalty, night service use, and adherence rates. A personalised approach should be applied to meet these client needs.

Drug developments for rare diseases

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Background: There are many rare diseases for which no speciality drug is available, but it is known from the literature that therapy is possible. In most cases, the rare disease therapeutic protocol is part of professional guidelines.
Aims: Therefore, we aimed in the Mikszáth Pharma-

cy, as far as our possibilities, based on the clinical evidence develop and produce niche drugs.
Methods: We have been able to count on the help of Hungarian and many foreign medical universities in the development of newly developed medicines. Our pharmacy laboratory has been designed to produce all pharmaceutical forms. Eg: injections, intravesical solutions, tablets, capsules, etc. The new active substances (Bismuth citrat, Zinci acetate) to be introduced were "positive list" after OGYÉI approval, and received TTT code and health insurance support from NEAK. In all cases, our new magistral formulations are tested according to the Pharmacopoeia. We also place great emphasis on checking the biocompatibility (pH, osmolarity) of all ophthalmic and intravesical preparations. In addition, we closely monitor the patients' drug therapy. Together with the treating physicians, we examine the clinical and therapeutic efficacy of our products.
Results: Over the past 12 years, we have developed a niche magisterial drugs against more life-threatening diseases. We currently provide nearly 3,500 patients in Hungary with our newly introduced drugs in the indications below:
– *Wilson's disease – Comprimata zinci acetas*
– *Helicobacter pylori infection – Second line eradication (Capsula bismuthi et metronidazoli)*
– *Nephropathic cystinosis -Oculogutta cysteamini*
– *Fusarium keratitis – Oculogutta argenti nitrici*
– *Acanthamoeba keratitis – Oculogutta polyhexanidi*
– *Stenotrophomonas maltophilia keratitis – Oculogutta/ Oculentum trimethoprimi et sulfamethoxazole*
– *Uveitis – Oculogutta/ Oculentum prednisolone*
– *Central hypogonadismus – Injection alfa-koriogonadotropini (grants specific aid to NEAK)*
– *Chronic bladder pain syndrome – Solutio GAG stratum restitutor cum adapter*
– *Status epilepticus- Solutio midazolam cum MAD nasal*
Conclusions: The magistral formulations developed and produced in the pharmacy laboratory are niche and indispensable for the continuous and safe supply of medicines.

New challenges in the pharmaceutical development

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The pharmaceutical companies working on the development of new medicinal products have to face continuously changing challenges. These changes have various reasons. In medicine, the background of many illnesses has been explored and become well understood, and this contributes to the efficiency of the pharmaceutical product development. The share of biological medicinal products – which require special technological apparatus and analytical knowledge – is expending, but even in cases of medicinal products with small molecule active substances, more advanced technological procedures are applied during development and production. New types of excipients appear which can also be used to modify or control the release and even the absorption of active substances. At the same time the regulatory requirements are getting stricter and to comply with these regulations means high cost and time in many cases. There are great expectations of the prices and differentiation of medicinal products by health insurance companies, doctors and even by patients as well. The pharmaceutical product development has to work in this multi-pole system and find the fastest and the most cost effective way to elaborate the preparation and to execute the economical commercial manufacture of new medicinal products which are modern, satisfy patients' need, and have the required quality as well. The pharmaceutical industry needs to investigate the efficiency of technological processes and the feasibility of commercial manufacturing, and meanwhile to pay special attention to the production cost and yield. New measurement techniques are involved in the development and production which help us to acquire deeper knowledge about our processes. The question is whether the pharmaceutical industry and education is prepared for these changes?

Possible service of hospital-based outpatient pharmacies: dispensing of medicines with special patient information requirements

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Background: Physicians working at the University of Szeged, Albert Szent Györgyi Health Centre („SZAKK") can prescribe medicines to discharged patients and to patients who seek medical care at the hospital's outpatient services. These prescriptions can be redeemed at the hospital's outpatient pharmacies but also in other community pharmacies.
Aims: To analyse the quantity and pattern of drug prescriptions issued by physicians working at the SZAKK.
Methods: The retrieve all prescriptions issued at the SZAKK during 2018 from the informatic system (e-MedSolution® Electronic Patient Workfilesystem) and transfer it to Excel. Drug were classified according to the WHO ATC system (version 2019). Drug prescription was quantified as number of prescribed packages and gross price.
Results: Slightly over than half million (594 thou-

sand) drug packages were prescribed during 2018, corresponding to 900 different active agents. Drug products of the „L" ATC main group (antineoplastic and immunomodulating agents) made up nearly 65% of all costs. Ranking active agents according to gross price, the top ten agents were: teriflunomide; fingolimod; somatropin; tacrolimus (oral); ruxolitinib; natalizumab; glatiramer acetate; alemtuzumab; sunitinib and mycophenolate mofetil. These active agents were marketed min. 5 years ago. Six agents have oral, 4 parenteral administration route.
Conclusion: Pharmacists working at the outpatient dispensing pharmacy of the SZAKK should be sufficiently knowledgeable about these medications and should work closely with the prescriber to optimise drug treatment.

Formulation of innovative ophthalmic preparations

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Background: The locally administrated ophthalmic formulations on the market have poor bioavailability thanks to the elimination mechanisms (reflex lacrimation and blinking) and barrier function of the eye. It would therefore be useful to design a new formulation which is able to prolong the residence time reducing the administration frequency; and are able to increase the penetration of the drug into the deeper layers of the eye (when not the eye surface is the site of action).
Aims: The aim of our study was to improve the bioavailability of poorly water soluble ophthalmic steroidal anti-inflammatory drugs (prednisolone and dexamethasone). Two different strategies were applied: 1) increase the residence time on the ocular surface using cyclodextrin modified mucoadhesive polymers; and 2) application of nano lipid carriers in order to increase the penetration of drug through the cornea.
Methods: To analyse the improved residence time and controlled drug release, rheological and mucoadhesive investigations, drug diffusion tests were applied. For the formulation and characterization of the nano systems, preformulation studies, and a 23 full factorial design were used, the advances of the nano formulations were evaluated by penetration and drug diffusion studies.
Results: The application of the mucoadhesive polymers can increase the residence time of the formulation on the eye surface, which is indicated by the mucoadhesive measurements. The combination of the mucoadhesive polymer with cyclodextrin can increase the solubility of the steroid drug, and the cyclodextrin immobilization can control the drug release. The application of nano lipid carriers enable to dissolve the lipophilic drug, which resulted 2-fold drug amount in the dissolution medium, and could help its penetration into the hydrophilic stroma in the cornea, which can serve as a depo for the further deeper penetration steroidal drug.
Conclusion: Both of the applied strategies can effective in ophthalmic formulations. In the first case, the improved residence time and the immobilization of the drug-cyclodextrin complex can the key factor of the effective controlled drug release. In the case of the second strategy, the improved drug solubility, the penetration enhancing effect of the nanocarriers can place these formulations into the innovative ophthalmic preparations.

Potential applications of BGP-15 in clinical cardiology -review of available preclinical data

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BGP-15 in heart failure and atrial fibrillation.
Growing incidence of heart failure (HF), especially the form with preserved ejection fraction (HFpef) defined as the presence of HF symptoms and elevated level of biomarkers with left ventricular ejection fraction (LVEF)>50% has recently been demonstrated. There is no specific therapy available for this entity. Atrial fibrillation (AF) is another global health problem with rapidly increasing incidence. Significant relationship between AF and HF and frequent coincidence of both with type 2 diabetes mellitus has also been established. The critical role of fibrosis in these pathologies has been suggested by imaging and laboratory tests. The drug candidate BGP-15, an insulin-sensitizer and heat-shock protein demonstrated efficacy and safety in patients with type II diabetes and in healthy controls. Further, this small molecule was tested in a rat model of diabetic cardiomyopathy and mouse models of both HF and AF. Significant improvement in diastolic function and attenuation of myocardium fibrosis were demonstrated in these preclinical investigations.

BGP-15 in inappropriate sinus tachycardia.
Inappropriate sinus tachycardia is defined as an elevated resting heart rate in the absence of an underlying cause and/or a rapid increase in the heart rate with minimal exertion. Available treatment with beta-blockers, Ca-channel blockers or the I_f channel-

blocker ivabradine often fail to provide sufficient symptom control and titration of beta-blocker to a sufficient dose might be limited due to significant hypotension. Result of animal studies suggest modest effect of BGP-15 on resting heart rate. Allosteric modulation of beta-receptors in the cell membrane as demonstrated by lipidomic investigations suggest that co-administration of BGP-15 and beta-blockers might be worth study in this difficult patient cohort.

Acknowledgement: GINOP-2.3.2-15-2016-00043, and the research was also financed by the Higher Education Institutional Excellence Programme (NKFIH-1150-6/2019) of the Ministry of Innovation and Technology in Hungary, within the framework of the Therapeutic Purpose Development thematic programme of the University of Debrecen.

Drug-device combination products in view of the new MDR (Medical Device Regulation)

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In recent years there has been an increase in the number of marketing authorisation applications (MAAs) and scientific advice requests where a medicinal product incorporates a medical device for the use of the medicine. The availability of commercialised devices with automated functions is increasing and this may benefit patients with regular and long-term dosing requirements in an outpatient setting, either by self-administration or with the support of a professional or lay caregiver. This reduces the burden on patients and on healthcare systems.

Given the wide diversity of devices supplied with medicinal products, the continuous technological developments and the differences in medical device and medicinal product legislation, the data supplied in the MAA dossiers is often inconsistent and incomplete. Therefore, EMA has decided to publish a guideline on quality aspects of the dossier requirements for drug device combinations (DDCs) to show that the they are appropriately designed and controlled and can be used correctly in the intended clinical situation.

The guideline addresses the new obligations in Regulation (EU) 2017/745 on medical devices, in particular the requirements under Article 117. According to this article the marketing authorisation application (MAA) should include a CE (Conformité Européenne) certificate or declaration of conformity for the device or, in certain cases, an opinion from a notified body on the conformity of the device.

Medical devices supplied as integral to a medicinal product, such as pre-filled syringes, inhalers, and auto-injectors, are more complex than container-closure systems, due to the associated delivery and measuring or metering function. Inappropriate use of these devices may compromise the safety and efficacy of the medicinal product and result in adverse drug reactions or medication errors. Complex DDCs have the highest risk of inappropriate usage.

Evaluation of fitness for the intended purpose (e.g. administration of a medicinal product) needs to take into account the quality aspects of the device in itself and its use with the particular medicinal product, as well as the complexity of the device component, the patient characteristics, the caregiver characteristics where relevant and the clinical situation in which the DDC is to be used.

Flow-through hydrotoxicology equipment for testing chemicals on zebrafish

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Background: Zebrafish (Danio rerio) has had the biggest carrier in the field of toxicological tests recently. In addition to its role in licensing various active agents, today, due to the large number of desease models produced, there have already been results obtained on zebrafish used in human medicine. Despite some variations between the methodologies of the treatments applied, in general, the treatment concentrations used should remain as stable as possible throughout the experiment in order to obtain reliable results. However, the implementation of this criteria in aquaous environment is difficult.

Aims: To solve the problem mentioned above, our goal was to develop an equipment suitable for hydrotoxicological tests which is also capable to maintain the treatment concentrations with the least human intervention ensuring reliable results during the experiments.

Methods: Our goal has been achieved by a system created to test pure agents and mixtures on aquatic organisms which is:

- *able to prepare specific concentrations or concentration-range from a previously prepared stock solution based on the given parameters by diluting the stock solution.*
- *Is capable to adjust the amount of solvent used in each test pool to the same concentration.*
- *Is capable to replace the test solution automatically at a set time in a static, semi-static, or flow-through system.*
- *Is able to investigate certain chemical and physical parameters of the test solution and of treating and purifying the effluent.*

– *Minimizes the risk of human contamination.*
– *Can be introduced for tests made in GLP (Good Laboratory Practice) systems.*

Results and conclusions: The flow-through toxicological equipment is suitable for performing zebrafish toxicology tests. The applicability of its final prototype has been verified by analytical and toxicological tests, which have already met the quality criteria of the most commonly used OECD standards in the case of water soluble substances.

New therapeutic possibilities of astaxanthin administration

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Astaxanthin (AX) a marine xanthophyll carotenoid is a powerful natural antioxidant which emerged in the spotlight due to its potential anti-cancer, anti-diabetic, anti-inflammatory, immune-stimulating effects. Here the effects of AX in skeletal muscles from young adult (4-5 months old) male C57Bl7 mice fed with AX for 4 weeks (AstaReal A1010, 0.05% w/w added in standard rodent chow) were evaluated. The actions of AX feeding on food intake, energy homeostasis, and the arcuate nucleus of mice expressing were examined. Furthermore, electrophysiological experiments were carried out on isolated canine ventricular myocytes acutely treated with 2.5μM AX.

At the end of the 4 weeks feeding period the body weight gain of the AX group was significantly less when compared to control (0.16±0.33 vs 1.22±0.31g, $p<0.01$) although the mice consumed roughly the same amount of chow. The voltage activation of calcium transients of single isolated *flexor digitorum brevis* (FDB) fibers of AX treated and control animals was identical. The mitochondrial Ca^{2+} uptake in FDB fibers upon repetitive stimulation was found to be less prominent in the AX group. The amplitude of *ex vivo* tetanic force measured on the *extensor digitorum longus* muscles was significantly higher in AX than in control (7.1±0.5 in CTRL vs 8.7±0.5 kN/m^2 in AX, *$p<0.05$). Neurons of AX supplemented mice displayed significantly greater frequency of spontaneous inhibitory postsynaptic currents (sIPSC). Similar, although weaker frequency increase was seen on POMC-positive neurons when AX was applied acutely. 77% of the GABAergic neurons displayed higher frequency of calcium transients, and a subpopulation of GABAergic neurons showed augmented excitability and received excitatory postsynaptic currents (EPSCs) with a greater frequency. In canine ventricular myocytes acute AX administration significantly decreased the APD50 and APD90 durations, as well as Vmax and the mid-plateau potential. Based on our results, AX improves tetanic force in skeletal muscles without affecting the ECC mechanism and exerts a protecting effect on the mitochondria against calcium overload. In neurons from the arcuate nucleus that play a cardinal role in the control of feeding AX increased the maximal AP and IPSC frequency. In cardiac myocytes AX shortened the duration of the APs which could have potential anti-arrhythmic implications.

Quality by Design and Process Analytical Technology in pharmaceutical development

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Background: Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. Process Analytical Technology (PAT) is defined as a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality. This paradigm change has the advantage of promoting a better understanding of the material characteristics and process parameters affecting the final quality of the targeted product, also brings a holistic and risk-based structured way of thinking into industrial manufacturing procedures. The so called "R&D QbD" is advised to be introduced into the early development phase of dosage form and manufacturing process design, including modern risk assessment and further quality tools.

Aims: The aim of this summary is to disseminate the knowledge and experiences of the R&D QbD model introduced into different challenging projects, such as designing colloidal carrier systems for nanomedicine use specially in case of peptide-protein drugs.

Methods: The main elements of "R&D QbD": Preformulation Design, Stakeholder Analysis, Initial Risk Assessment, Composition & Process Design, Design of Experiments, Design Space Development, Control Strategy.

Results: The selected experimental examples prove the efficiency of involving the elements of QbD in composition design and preparation of non-biological and biological complex drug formulations.

Conclusion: Application of the methodologies of "QbD" and "PAT" facilitates knowledge and technology transfer from early phase of pharmaceutical development to industrial manufacturing, resulting

quicker market access e.g. in case of non-biological and biological complex drugs for unmet clinical needs.

How can I improve the patient safety as a pharmacist?

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Patient safety is a serious global public health issue. That was first discussed during the World Health Assembly in 2002 since then WHO have been developing policies and publishing declarations, guides and brochures in order to draw attention to patient safety. In the past decade projects focusing on patient safety were carried out one after the other in Hungary as well, to empower care givers and institutions in the national health care system. Safe medication is one of the most important aspect of patient safety that can be guaranteed by prevention of medication error. Pharmacists have a key role both in outpatient and inpatient settings. In order to do that, pharmacists need to develop their knowledge and skills. The presentation will cover the methods offered by WHO which have appeared in the Hungarian developments and the ever more popular patient safety programmes.

The health care is a very complex system therefore it involves risks, but it can be made safer by recognising the potential errors, and by developing systems and strategies to learn from mistakes so as to minimize their occurrence and effects. As health-care workers it is important to be mindful of situations that increase the likelihood of error for human beings. For improving patient safety, we have to develop a work culture that encourages the reporting of adverse events and near misses in health care. The aim is to understand the nature of error and how health-care providers can learn from errors to improve medication safety.

Health care is rarely carried out by single individuals. Safe and effective care is dependent not only on the knowledge, skills and behaviours of workers, but also on how those workers cooperate and communicate in the work environment. For example only a part of the prescribing errors that are made reach patients; the others are caught in time by pharmacists and other health-care workers. This fact underscores the importance of teamwork. We understand and use the other tools of patient safety developing and we avoid to reliance on memory we simplify and standardize processes and procedures, use checklists and do not only reliance on vigilance.

Possibilities of social media in the improvement of adherence

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Background: The success of a medication lies not only within taking the medicine, but more within the adherence of the patient. Therefore, the patient's lifestyle is not marginal in the outcome of the therapy, the enhancement of the quality of life.

Aims: An outstanding task of the pharmacist is to support the adherent behaviour of the patient.

Methods: I have evaluated the role of online pharmaceutical consultation and the effects of online presence in the analyses of several online surveys. These show unequivocally that the online presence of the pharmacist helps medical professionals to be the primary source of information. Besides, great responsibility lies within providing authentic information.

Results: I have the greatest experience in connection with consultation on Facebook, since 2014. I would like to present its development, and what steps have been made in order to make the process more professional. Today, this consultation is not the task of an individual, but the cooperation of 7 pharmacists. We provide answers to more than 6,500 persons' questions almost every day, within 12 hours. We strive to encourage people to ask questions, our principle is that there is no stupid question.

Conclusion: When answering, comprehensibility, up-to-date knowledge and the possibility of a conversation between questioner and professional are very important. This makes the clearing of vague areas and follow-up possible. The process being written is very helpful in this, as this makes history and anamnesis accessible. All this enhances the patient's trust in the professional, which enables us to deal not only with questions of therapy, but also improve the patient's adherence.

Experiences with the website of the Hungarian Society for the History of Pharmacy

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The Hungarian Society for the History of Pharmacy started a systematic development of its website (www.gyogyszeresztortenet.hu) in 2013, which opened a new era in the history of pharmacy in Hungary. We currently have full pdf copies of about 320 books, 52 doctoral theses and diploma works, more than 2000 articles (an estimated 90% of all papers in the last 60 years), a Lexicon of more than 350 out-

standing Hungarian pharmacists, a Lexicon of more than 1000 old drugs based on the labellings of pharmacy jars, journals, hundreds of photos of old pharmacy equipment, old industry-made preparations and prescriptions, in addition to useful links (such as links to our fellow Societies). everyday newsflow. Since these pdf files have been prepared using optical character recognition, by a built-in Google search engine researcher of our website can search for any information simulteneously in more than 100,000 pages of highly diverse literature sources. Our website even provides information to people searching Google or other search engine in general, having heard nothing about or website before. Consequently, we have been contacted by individuals in and outside Hungary who have found genealogy and other data, and the very efficient identification of any keyword or expression stimulated research and publication activity as well. For example, this electronic researh tool opened way to co-operating with more than a dozen pharmacy student to puzzle out the meaning of acronyms of materia medica on the labels of old pharmacy jars and glassware. This presentation intends to share our experiences in developing and using electronic research in history of pharmacy.

Examination of the effectiveness of medication review done by pharmacists in Hungarian community pharmacies

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Background: According to the definition of Pharmaceutical Care Network Europe „Pharmaceutical Care is the pharmacist's contribution to the care of individuals, in order to optimize medicines' usage and improve health outcomes." The main tool to this activity is medication review, which is the evaluation of the patients' medicines. A successful review can reveal Drug-Related Problems (DRP), which are „situations in which in the process of use of medicines cause or may cause the appearance of a negative outcome associated with the medication".
Aims: The aim of our study is the qualitative and quantitative description of DRPs detected by community pharmacists, including interactions, and to confirm the importance of patient education related to medication review.
Methods: Data were collected from patients with polypharmacy by resident community pharmacists within a project from October 2017 to March 2018 practicing medication review. Patients's knowledge of medicines was measured by a self-developed questionnaire survey, while the responses were recorded through patient interviews. The pharmacists categorized the DRPs uniformly (DRP1-DRP6) and determined the root causes as well. The frequencies of the drugs and drug-classes causing interactions were determined and all the interactions were classified by clinical risk as well (UpToDate Lexicomp®)
Results: In the project, 763 patients were enrolled by 78 pharmacists in 78 pharmacies. The average number of products taken by the patients was 9.34, which value did not change significantly. The average knowledge of medicines increased by 3.8% from the initial 67.9%. On average 1.1 DRP per patient were reported, mostly due to interaction risk (41.5%). The overwhelming majority (68.5%) of interactions were between two prescription medicines. The most commonly reported interacting agents were perindoprile, amlodipine, acetylsalicylic acid, metformin and bisoprolol. 20.9% of the interactions carried a serious clinical risk, while 30.7% of them were irrelevant clinically. The most common intervention of the pharmacists was patient education (29.2%).
Conclusion: The results of this research confirm that the application of the mentioned pharmaceutical methodology can improve patients' knowledge of medicines and that pharmacists are able to reveal several DRPs that would remain hidden without the work of the pharmacist. Our results provide a good basis for developing a uniform procedure for medication review in Hungary.

New target in the tocolytic therapy: aquaporin-5 water channel

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Background: The aquaporin (AQP) water channels are small hydrophobic integral membrane proteins. Most of them are expressed in the female reproductive tissues and they play important role during pregnancy. We proved in our earlier study, that AQP 1, 2, 3, 5, 8 and 9 are detectable in the late-pregnant rat uterus and the AQP5 expression showed a dramatic downregulation on the last day of pregnancy. Moreover, our results lead us to suppose that the AQP5 expression is regulated by oxytocin and female hormones.
Aims: We hypothesized an osmotic pathway – through AQP5 – might have influence on the changes

in transient receptor potential vanilloid 4 (TRPV4) function and uterus contraction. Our aim was to determine the possible role of AQP5 in this osmotic regulation of TRPV4, thus in pregnant uterine contraction.
Methods: The expression of the TRPV4 and AQP5 were measured by RT-PCR and Western blot techniques for during pregnancy in rat uterus. Their localization in pregnant uterus was determined by immunohistochemical studies. The role of TRPV4 in uterus contraction was investigated in an isolated organ bath system. In vitro uterus contractions were stimulated with potassium chloride and its effect was investigated with the selective TRPV4 agonist (RN1747), antagonist (RN1734) and citral (3,7-dimethyl-2,6-octadienal) which is the active ingredient of lemongrass oil and lemon peel.
Results: The TRPV4 expression continuously increased from day 18 to the last day of pregnancy. We determined an inverse correlation between the AQP5 and TRPV4 mRNA and protein expression. The co-expression of TRPV4 and AQP5 was found in the late pregnant uterus tissue. The TRPV4 antagonist significantly decreased the uterine contraction; in contrast the TRPV4 agonist had no effect but induced the contractions in high dose. Citral treatment induced uterus relaxation on gestational day 22.
Conclusion: We presume the decreased AQP5 expression induces a hypertonic stress, which activates TRPV4 and increases uterine contraction on the day of labor. A potential hormone regulated cooperation exists between the AQP5 and TRPV4 expression. Based on these results, we acquired new information about the mechanism of birth and this link between AQP5 and TRPV4 could be a new target in tocolytic therapy.
Acknowledgement: This work was supported by the National Research, Development and Innovation Office, Hungary (grant FK19-132499).

Dimensions of safe pharmaceutical supply

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Nowadays medicine is an indispensable tool of healing. A constant, safe and cost-efficient pharmaceutical supply chain is an essential part of a healthcare system operating efficiently at a high standard.
When we talk about pharmaceutical supply, we distinguish between public and institutional pharmaceutical supply. The safety of both can be assessed from different perspectives; from the perspective of the recipient of the service (the patient), the service provider (public/ institutional pharmacy), the financer or the authority, but the goal should always be the same. Right quality, cost-effective medicine should be provided to the right person at the right time.
The area of pharmaceutical supply cannot escape development, innovation and accelerating life. Despite this, it is of great importance that pharmacist-patient meetings continue, and pharmacists find their place among the changing circumstances. It is essential to eliminate contingencies in the area of pharmaceutical supply as well, in order to have as many controlled processes as possible, in which the same input results in the same output. The diversified activities of pharmacies require healthcare providers to operate an internal quality control system. This is complemented by the external quality control system which is operated by the designated public health authority.
The Chief Pharmaceutical Division – as the authority responsible for the supervision of pharmaceutical retail (designated public health authority) – is also an integral part of the system of safe pharmaceutical supply. Because its activity is that of an independent, objective helper, it operates as an external control system. It feeds back the experience of on-site inspections in two directions: to the organization providing the health care service, and also to the legislator. The aim of the two-way feedback is to ensure that the service providers comply with current laws in all cases, and that the legislation is also suitable for regulating the sector.

OGYÉI website security incident – behind the scenes

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Background: In october 2018 the website of the National Institute of Pharmacy and Nutrition (OGYÉI) has been successfully attacked. As we are the licensing authority for pharmaceuticals in Hungary, the incident received wide media publicity after being announced on our website.
Aims: My aim is to provide information on the institute's IT security goals and the current state. I will talk about the method used by the attackers and the conclusions we've drawn. The presentation will contain all the necessary information on IT security and information security so that no prior knowledge will be needed in the field to understand it.

Survey on antidiabetics and complementary and alternative medicines among NIDDM patients, ratio of adverse drug reaction and the outcome with a voluntarily completed anonymous questionnaire

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Background: Type 2 Diabetes mellitus (T2DM) is a

major public health challenge, both in developed and developing countries. T2DM leads to several complications e.g. macrovascular and microvascular diseases. Pharmacological and non-pharmacological management are used to improve glycaemic control in patients with T2DM. Complementary and alternative medicines (CAM) for the treatment of T2DM are probably based mainly on treatment of its obvious symptoms of pronounced thirst and polyuria. Nature is an outstanding source of antidiabetics and plants may be valuable dietary supplements to improve blood glucose control and prevent long-term complications in T2DM. Co-administration of herbal products with medicines may result in unfavourable interactions.

Aims: Collecting data about the use of CAM among T2DM patients. Besides this, data about the antidiabetics, its adverse drug reactions (ADR), outcome, patients' demographic characters, lifestyle, and other health behaviours were also collected.

Methods: A non-interventional study with self-developed questionnaire was used accepted by the Regional Ethical Committee. It was distributed among adult NIDDM patients who have suffered from cardiovascular consequences. A database was compiled from the anonymous questionnaires filled in voluntarily by the patients. Basic statistics were used to analyse database.

Results: A total number of 101 questionnaires were filled in. Mean age was 65.7 ± 10.9 years. Of the patients 57% were male. Average body weight was 85.5 kg. Eighty-one percent of patients said that they follow certain diabetic diet to control their blood glucose levels. Nine percent of patients reported last measured blood glucose level higher than 10 mmol/L. Concerning last measured HbA1C value, 16% of patients had higher than 6.5%. Eight patients have reported ADR due to metformin. Twelve percent of patients use CAM because they believe in CAM. Two out of them have reported ADR. Mean cost of CAM therapy was 3120 HUF/month.

Conclusion: Our findings confirmed that most of the patients adhere to the recommendations on diet. Unfortunately, high blood glucose level and HbA1C lab findings were reported which suggest ineffective treatment or non-adherent patients. CAM users are minor portion in this population. These facts support the idea that patients' education and motivation is essential. Clinical pharmacists should contribute in these activities and enhance patients' adherence in order to improve patients' quality of life.

The greatest challenge of the 2020s – medicine shortages

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Today one of the greatest challenges of the supply of medicinal products is how to handle medicine shortages. It is not a new phenomenon, and is neither solely Hungarian nor European, but a global problem. In order to elaborate the appropriate responses, we have to come to an agreement in a number of fundamental questions:

- *How to define medicine shortage;*
- *What are the causes of the shortages;*
- *What is the task of the participants;*
- *How is it necessary or possible to restructure the medicine supply / support system to be able to reduce the number of shortages in the long term, and eliminate the causes – is there a solution to this at all?*
- *How can a shortage be handled so that*
  - *Patients receive the appropriate therapy under all circumstances;*
  - *No reduction in confidence in healthcare occurs;*
  - *The solution is cost-effective and safe for all participants;*
  - *The efficient medicine supply framework established in Hungary does not become distorted.*

The lecture aims at finding answers to these questions and also presents the solution proposals coming from certain European Union Member States.

Pharmacokinetics and tissue distribution of PET radiotracer labelled β-cyclodextrin derivatives

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Background: Hydroxypropyl-β-cyclodextrin (HPBCD) and Random Methyl-β-cyclodextrin (RAMEB) are widely used in drug formulations and recently orphan designation was granted for HPBCD in the treatment of Niemann-Pick disease, type C. HPBCD is considered to safe, but the exact mechanism of action and side effects are not completely understood. Labelled cyclodextrin derivatives are required to reveal the biological activity and in vivo distribution by imaging techniques.

Aims: The aim of our study was to synthetize the 68Ga-labelled NODAGA-HPBCD (68Ga-NODAGA-HPBCD) and 68Ga-labelled NODAGA-RAMEB (68Ga-NODAGA-RAMEB) and test their pharmacokinetic properties and in vivo distribution by positron emission tomography (PET).

Methods: We conjugated HPBCD and RAMEB with NODAGA and labelled with Gallium-68 (68Ga). The radiochemical purity and in vitro stability were determined and found to be suitable for in vivo application. For in vivo dynamic and ex vivo biodistri-

bution studies we used control BALB/c mice, while for the in vivo tumor model we used SCID mice.
Results: 68Ga labelled NODAGA-HPBCD and RAMEB were mainly excreted by the kidney, due to their hydrophilic properties. The accumulation of the radiotracers in abdominal organs was low, and no uptake was found in the brain. Interestingly elevated uptake was observed in the lung and in tumors.
Conclusion: In conclusion 68Ga-NODAGA-HPBCD and 68Ga-NODAGA-RAMEB were successfully produced for the first time and tested in vitro and in vivo. The outcome of our study indicates that the in vivo behaviour of radiolabelled cyclodextrins can be examined by PET techniques, thus these derivatives are suitable for further pharmacokinetic and cancer targeting measurements.

Acknowledgement: This study was supported by FK_17 (FK124634) research grant of the National Research, Development and Innovation Office, Budapest, Hungary and by the János Bolyai Research Scholarsip of the Hungarian Academy of Sciences (BO/00290/16).

History of CERTA Laboratory between its establishment in 1924 and nationalization

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Background: Development of the Hungarian pharmaceutical industry started in the middle of 19th century. In the interwar period there worked 57 pharmaceutical factories and manufacturing laboratories in Hungary. Pharmaceutical industry played an important role in the general economics and supplying of pharmacies.
Aims: To characterize the establishment and operation of the CERTA Laboratory in Budapest and contribute to the history of Hungarian pharmaceutical industry.
Methods: Methods of historical research were applied to reconstruct the working and professional activities of CERTA Laboratory. As main sources were used archival documents and other historical sources published in the studied period – pharmaceutical journals, statistical publications, photographs, maps.
Results: The history of CERTA Laboratory has been studied in the period between its establishment in 1924 and nationalization in 1950. CERTA was specialized in manufacturing of injections. Operation of the Laboratory reached its highest level in the 1930s when the professional management members were Mária Quittner and Tamás Löcherer. Several new machines, processes of production and quality control were introduced to the manufacturing process to produce high quality and safe medicinal products.
Conclusion: Some aspects of development of the pharmaceutical industry in Hungary are characterized on a specific example of a smaller manufacturing company – CERTA Laboratory established in the interwar period. Its 26-years existence represents every important development trends of industrialization in pharmacy including founding process, expansion, modernization, decline of production and damage caused by war, renewal of operation, and nationalization.

Development of biological drugs

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Gedeon Richter Plc., Debrecen

Education of future pharmacists: visions and challenges

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The education of pharmacist is always a hot topic. Students frequently feel that they must study too much and additionally, a given proportion of the curriculum seems unnecessary or useless. On the other hand, teachers frequently feel that the capacity and the professional interest of the students are constantly decreasing. All these feelings may be rooted in the shortfall of the educational system, the system that is the meeting point for teachers and students. Nobody debates that our world and the generations are changing quickly, but what about our educational system? It is easy to hind behind laws and rules to avoid fundamental changes, but who will response to the real professional needs?
This section is not to praise but to promote the education of future pharmacists. Deans and leaders of pharmacy faculties, student representative, pharmacist top athlete will flash their ideas and visions about the desired future of undergraduate and postgraduate trainings of pharmacists. The lectures will be continued in a round table discussion with the participation of the ministerial commissioner for medical education. The audience will have limited possibility to comment and ask during the round table discussion.

The role of health technology assessment to optimize the societal level benefit of the treatment of the biological agents in immune mediated inflammatory diseases

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Background: Health economics, including health outcome evaluation is playing an important role to

improve and optimize the health gain in patient and societal level.
Aims: There are number of challenges to face in improving health of the public.
Methods: The life expectancy of the population and the (well) treated patients are rising. The increasing prevalence of various chronic diseases and health states, due to improvements in treatment has led to an increase in the number of patients requiring treatment. Growing number of incurable and unpreventable diseases, such as rare diseases, blood disorders (chronic lymphocytic leukemia for instance) are becoming ‚treatment related' chronic diseases (similar to rheumatoid arthritis, hypertension or diabetes). Growing number of patients suffering in chronic diseases and the rising number of multiple co-morbidities, due to the increased life expectancy, creates escalating long-term financial commitments/ burden on the societies, families and individuals.
Results: More resources and more sophisticated resource allocation decision making is needed to achieve efficiency gain and to maintain Universal Health Coverage. Health Technology Assessment (HTA) is a tool for informing decision-making on value for money of publicly reimbursed health technologies and their conscious introduction and use. This is one possible avenue to increase efficiency of health systems. In most of the European countries all medical services claiming public funds are subject to HTA.
Conclusion: Another important challenge is to achieve better equity and access in Europe and elsewhere. Biological drugs for instance are recognized as important treatment options in European clinical guidelines in rheumatology, gastroenterology, dermatology and hematology. Despite this, the impact of biological therapies is often diminished in clinical practice by (huge) inequalities in patient access. Significant health benefits would result from better reimbursement and improving adherence to existing treatments, these are among the key sources today in improving health of the public.

The National eHealth Infrastructure (EESZT) from a policy perspective: challenge and opportunity

HANKÓ, Z.
Hungarian Chamber of Pharmacists, Budapest

The e-Prescription system, the first service of EESZT was initiated on 1 November 2017. It required pharmacies to be the first of the healthcare providers to completely join the EESZT. The relationship between the EESZT and the pharmacies has been the focus of attention ever since.
In addition to the common expectations (e.g. continuous, safe and fast operation, data protection) towards the EESZT from different parties (politics, EESZT system developers, IT service providers, pharmacies, healthcare providers and patients), pharmacies have also required the followings since the beginning: uniform master list and database, secure NEAK settlement, prescription writing in accordance with the provisions, and user-friendly operation.
In the upcoming period, emphasis will be placed on the development of other EESZT functions, but it is also important that medicine- and pharmacy-related developments continue. Such development could be the EESZT support of periodic safety update validation and a record of patients' past medications. These are important features from a treatment adherence perspective. The EESZT can help to harmonize medications for inpatient and outpatient care, as well as to achieve health and economic objectives. Trade and utilization analyses can also support the management of pharmacies. Today, pharmacies provide the same data to multiple locations, but here is a chance for simplification.
To materialize all these opportunities, close cooperation is needed with all parties in the system. Attention must be paid to ensure that developments are carried out in a targeted manner and not according to particular interests.

Hungarian dream and American reality in child healthcare

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Last fall, I had the opportunity to spend three months at Cincinnati Children's Hospital Medical Center in Cincinnati, Ohio. The hospital is the second largest and the third best (Honor Roll) Children's Hospital in the US, covering the entire vertical of child healthcare. Every year, more than 1.3 million children are provided with 670 beds and 400 home-care facilities, with more than 15,500 employees. During the study visit, I had opportunity to know widely to the healing work, patient education and disease prevention work as well in the hospital.
Of course, neither the size of our children's hospitals, the structure of childcare, nor the financial resources availability are comparable to those in the US. However, there are some welcome similarities, many practices to consider that possibly could be implemented at home. There are serious and less serious deficiencies in today's Hungarian child healthcare.
As a clinical pharmacist, I went through many of the hospital's units and departments and looked at the work there. I often watch with envy of the patient and drug safety infrastructure, human resources, IT system, well-organized and coordinated work, and the work of multidisciplinary teams in healing.

It has been a pleasure for me to see that working together and appreciating common values stemming from a sense of vocation, together with the recognition of it, makes healing work successful and satisfies the children and their parents and the staff who work with them.
I have a "dream" to me as well, that must surely be a dream for all of us, and we are no further from the realization of our dream than Martin Luther King when he gave his famous speech in 1963. I have a dream that one day, maybe in the time of our children, or maybe only of our grandchildren, the Hungarian healthcare will reach what I saw and experienced in Cincinnati.

Psychosis spectrum disorders – a contemporary approach to the treatment of schizoprenia and bipolar disorder

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Background: Previously schizophrenia and bipolar disorder was considered as distinct disorders, however according to the contemporary view of psychotic disorders they can be rather described along a spectrum.
Aims: Contrary to the former categorical approach, biomarker research on various psychotic disorders shifts thinking toward a dimensional approach.
Methods: The various psychotic disorders overlap in many aspects and share common biomarkers.
Results: According to our present knowledge, psychosis spectrum disorders are considered to be neurodevelopmental disorders, in which the interaction of biological-genetic and environmental factors plays an important role. Recent results also highlight the synergistic effects of various environmental factors. As a result, the staging approach in treating psychotic illnesses is increasingly emphasized.
Conclusion: According to this approach, psychotic disorders progress in stages with increasing severity, and efforts must be made to provide the best evidence-based treatment appropriate to the given stage.

Contained & safe handling of hazardous bulk solids

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In this presentation we will introduce you to the wide Containment-topic. You will learn about the definition of containment, the key-issues and initial steps of planning a Containment project. Further topics will be the threshold-classification of solids and other bulk materials and how you choose the right equipment for these solids. We will provide an overview about different basic thresholds and how they are calculated as well as a critical view on safety data sheets. Furthermore, you will be taught about important steps of process planning during a containment project and where potential risks occur. To show you the risks, you will see a typical pharmaceutical example process. To qualify machines and to validate processes we will discuss the Smepac-test. SMEPAC means: Standardized Measurement of Equipment Particulate Airborne Concentration. It is designed to give you an orientation and a method to validate suitability of the equipment for the intendent use with dangerous products. One of the most underrated topics is the "human factor". We will discuss some interesting insights about planning ergonomic and easy to use equipment. Finally, we will talk about the cleaning process as well as different cleaning methods like WIP and CIP.

Dead end or inadequate regulatory environment? – The current issues of the legal framework governing the distribution of herbal products

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Background: Nowadays it requires extreme effort if a company intends to place herbal medicinal products (including traditional herbal medicinal products) on the Hungarian or European market. Although the inventory of herbal substances having known or assumed to be known efficacy proved by published clinical studies contains numerous substances for various therapeutic areas, the real challenge is (even for the largest pharmaceutical companies) to find herbal active substances (herbal drugs or herbal drug preparations as defined in the European Pharmacopoeia) of adequate quality manufactured and documented according to the EU Good Manufacturing Practice (EU GMP) requirements.
Aim: The aim of the presentation is to review the advantages and burdens of the possible legal categories available for herbal products. Furthermore, to provide practical advices for healthcare professionals and consumers on the selection of efficacious herbal products with satisfactory quality and safety.
Methods: The legal frameworks for authorisation/notification and distribution of herbal medicinal products and herbal food supplements are compared with special focus on the quality requirements of the herbal substances. The consequences of the revealed differences are analysed in order to evaluate the current and future prospects of herbal remedies.

Results: The burden to put herbal medicinal products on the market is so high that new herbal (traditional herbal) medicines are hardly available while the number of herbal food supplements increasing continuously. Additionally, the compositional and quality aspects of the herbal food supplements are not adequately controlled by the current European legislation allowing the marketing of products with questionable value.
Conclusion: It seems that the current pharmaceutical legislation is not appropriate or perhaps not intended to provide solution for fulfilling the growing consumer demand on herbal products. In contrast the shortcomings of the food-supplement legislation ensure excellent possibility for those who have recognised the real or presumed business opportunities in the application of herbal substances without actually facing the threefold requirements of quality, safety and efficacy.

Advanced pharmaceutical care for interstitial cystitis

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Background: Interstitial cystitis (IC) is a barely known disease that causes urinary problems and pain. The number of people affected in Hungary is estimated at 20,000. Currently, 600 patients have been diagnosed. The cause of IC is unknown. It is due to the thinning of the bladder surface mucosa, which is made up glycosaminoglycan (GAG). This process can lead to the development of sterile inflammation. If this condition remains untreated, the disease can lead to cystitis and kidney failure. We believe that pharmacists can take part in recognizing and treating this disease because a lot of patients arrive at the pharmacy with urinary complaints.
Aims: Therefore, our goal is to develop a protocol that will help to recognize the symptoms of the disease and will guide the drug therapy in patients' care.
Methods: During the planning process, we took into account our existing professional guidelines, consulted with the specialist for treatment and conducted our own questionnaires.
Results: For mild symptoms of patient with IC: we can recommend a special IC diet, which has been prepared based on a number of foreign diets and an own questionnaire. For moderate symptoms of patient with IC: in addition to diet, medication is also important. The goal is to alkalize the urine to reduce the irritating effects of the urine. Oral GAG-layer regenerating drugs such as chondroitin sulphate and collagen-containing tablets can also be taken and a small amounts of vitamin C is necessary for proper incorporation of these compounds into the GAG layer. Initial treatment can be supplemented. In case of severe symptoms of patients with IC: the most effective is the combination therapy (oral and topical). In this way, combined treatment and regeneration of the GAG layer is expected. In addition to oral drugs, the use of intravesical solution containing GAG layer components may help in the regeneration process. If no satisfactory result is achieved, it may be supplemented with symptomatic treatment. We may suggest strong analgesics, antidepressants and muscle relaxants.
Conclusion: IC is a severe autoimmune disease with a high prevalence in Hungary and a pharmacist's role in the care of this condition could be decisive. Many patients visit pharmacies with urinary problems. Based on the newly developed algorithm, pharmacists will be able to recognize IC and refer the patient to a specialist, also manage the drug therapy and the proper diet.

Experiences in the treatment of pregnant women with epilepsy in the last decades

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Background: Epilepsy is a complex issue that has an impact on the patients' quality of life especially among women of childbearing age. Fertility is significantly lower among patients with epilepsy. The underlying pathophysiology is an endocrine disturbance. Hormonal changes particularly during pregnancy may influence the seizure frequency. Controlling and preventing seizures are essential for both mother and foetus. Antiepileptic drugs (AED) might be linked to congenital malformation (CM) mainly in a dose-dependent manner. Treating epilepsy means a life-time treatment, so real-life studies are important.
Aims: Our aims were to analyse patients' history, AED treatment of women with epilepsy and the outcome in terms of pregnancy.
Methods: East-Hungarian Epilepsy Database (from 1992) was created in order to analyse the data of patients through their case histories from out-patient files. Basic statistics were used to analyse database.
Results: There were 112 pregnancies. Number of deliveries, miscarriage and artificial abortion were 88, 17 and 7, respectively. One third of the patients has not taken AED and remainders have received monotherapy and bitherapy. Three pregnant patients have stopped their AED arbitrarily. During organogenesis, the most common AEDs were carbamazepine

and lamotrigine. Newer type AEDs were preferred to prescribe for those who were regularly checked-up. No CM was confirmed. Seizure frequency has not changed during the pregnancy. One stillbirth was registered. One foetus has died at 24 weeks of gestation due to asphyxia in preeclampsia. In a twin pregnancy, placenta detachment has occurred. Only one patient's outcome was related to epilepsy who had four times generalized tonic-clonic seizures during pregnancy, she was non-adherent. Seven patients during their pregnancies did not visit an epileptologist at all or only after completed 26 weeks of gestation. After the delivery, AED dosage has been increased in three cases and decreased in four cases. Since newer type ADEs were marketed, the approach to pregnancy changed even from the point of view of patients.

Conclusion: Frequency of miscarriage was quite a same and artificial abortion less frequent among epileptic patients than in the population. Despite of known teratogen effects of some AEDs, CM were not identified in our database. Our findings highlight the importance of continuous care and established AED treatment in pregnancy. Clinical pharmacists may play a role in patients' care in epilepsy treatment besides the epileptologist.

Development of vaccines and vaccines for pandemic threats (in particular for COVID19)

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Vaccines, currently used for prophylactic purposes, prevent more than three million deaths every year from diseases like diphtheria, pertussis, tetanus, poliomyelitis, measles and influenza.

The general six stages of the development of a new vaccine are: i) Exploratory stage; ii) Pre-clinical stage; iii) Clinical development; iv) Regulatory review and approval; v) Manufacturing; vi) Quality control. Clinical development is a three/four-phase process. During Phase I, small groups of people receive the trial vaccine. In Phase II, the clinical study is expanded. In Phase III, the vaccine is given to thousands of people and tested for efficacy and safety. Many vaccines undergo Phase IV formal, ongoing studies after the vaccine is approved and licensed. Phase IV studies, also referred to as postmarketing surveillance studies (PMS). These processes are very similar to drug developments.

However, there are several differences compared to drug development, namely: i) unlike drugs, which are given to patients, vaccines are received by healthy individuals, thus the safety margin should be very high; ii) as vaccines have to be stored under refrigeration, there are always logistical challenges during clinical trials; iii) Adjuvants are incorporated into vaccine formulations to modulate and improve the immune response (antigen/adjuvant formulation are important aspects of clinical development); iv) The immune response primarily measured during early stages of vaccine development (Phase I/II) should evaluate: Humoral/ cell-mediated/ cross-reactive antibodies or immune complexes/ „immune landscape".

A challenge in responding to pandemic diseases is that vaccines may not exist for them. For newly emerging threats without licensed vaccines, such as SARS, MERS, Marburg virus, Nipah virus, SARS CoV-2 and the like, the time required to develop and produce a safe, effective vaccine is unknown and would depend on the nature of the threat and the state of current vaccine research for that threat. In almost all cases, several months would be needed to respond with the first doses of vaccines.

Unfortunately, six month later than WHO declared the public health emergency of international concern (27/01/2020) there are five important questions, essential for vaccine development that remain open for scientists, namely: 1) Why do people respond so differently to infection? 2)Has the virus developed any worrying mutations? 3)How well will a vaccine work? 4)Can we develop immunity and if so, how long does it last? 5)What is the origin of the virus?

Until a safe, effective vaccine was ready, other public health and medical measures (social distancing, quarantine, and aspecific medications) would need to be employed to try to limit disease spread.

Pharmaceutical technological aspect of magistral formulations in Hungary. Storage conditions, incompatibilities and expiry dates of often Used magistral preparations

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Background: In Hungary magistral preparation work is a determinative and traditional part of pharmaceutical activity. The reformation of Formulae Normales is a topicality of today. It often occurs that incompatible compositions or industrial preparation containing magistral compositions are produced in Hungarian pharmacies. In unique magistral production the uncertainty of expiry dates is often experienced.

Aims: Our aim was to choose a frequently applied active pharmaceutical ingredient (API) in magistral compositions which causes incompatibility prob-

lems and to work out an investigation method to determine and explain the changes. Further aims were to make stability investigations with magistral preparations at different storage conditions. With these date we could calculate the exact expiry date of these productions.
Methods: The applied methods were UV-VIS spectroscopy to determine the API content, X-ray powder diffraction, Raman spectroscopy and differential scanning calorimetry to detect the physical and chemical changes of the samples and dissolution and diffusion investigations to model the samples properties in in vitro conditions.
Results: Our results show that investigated APIs causes a lot of incompatibility problems in magistral forms. These changes can be organoleptic detectable and masked also. They can be followed instrumentally well. The stability or instability of these special forms modifies the correct storage conditions. The rethinking and the differentiation of expiry dates is needed also.
Conclusion: The instability of magistral preparations can cause series application problems and inaccuracies in treatment. In this way we have to recognise, clarify and treat appropriately them. Our work's results can help to solve these problems in pharmacies.

Preclinical studies of the nicotinic-acid derivative BGP-15

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Background: Increasing evidence suggests that small molecule BGP-15 improves muscle function, and reduce arrhythmias in disease models; however, its exact cardiovascular effects and mechanism of action are still not clear.
Aims: Our aim was to evaluate the effects of BGP-15 in different animal models. Mechanistic and molecular biology studies were aimed to particularly describe its actions on the cardiac function and signal-transduction pathway.
Methods: Rabbits suffering atherosclerotic cardiomyopathy, Zucker Diabetic Fatty (ZDF) rats, and Goto-Kakizaki rats were used as models for the preclinical experiments. Echocardiography was performed on the animals to assess acute, mid-term and chronic effects of BGP-15. Moreover, thoracotomy was also performed, then the vascular status of rats was evaluated using an isolated aortic ring method. Furthermore, endothelium-dependent vasorelaxation was investigated on isolated aortic rings. Western blot and ELISA methods were carried out to evaluate the expression and activity of mitochondrial proteins, cardiac enzymes.
Results: BGP-15 significantly improved diastolic dysfunction both in rabbits, ZDF, and Goto-Kakizaki rats. Vascular status was unaffected, but fibrosis improved after the treatments. The drug restored mitochondrial function in ZDF rats and increased survival rate. BGP-15 restored diastolic parameters and improved Tei-index compared to untreated Goto-Kakizaki rats. Vascular status was unaffected by BGP-15. Expression of vasodilator-stimulated phosphoprotein (VASP) and phospholamban (PLB) increased in BGP-15-treated rats, in comparison to the diabetic rats.
Conclusions: GP-15 significantly improves cardiac function in different disease models by exerting multiple actions. Determination of the molecular target of the drug candidate merits further investigations.

Acknowledgement: GINOP-2.3.2-15-2016-00043, and the research was also financed by the Higher Education Institutional Excellence Programme (NKFIH-1150-6/2019) of the Ministry of Innovation and Technology in Hungary, within the framework of the Therapeutic Purpose Development thematic programme of the University of Debrecen.

Novel drug candidates for neuropathic pain: small molecule somatostatin 4 receptor agonists.

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Background: Treatment of neuropathic pain is an unment medical need. Somatostatin released from capsaicin-sensitive peptidergic nociceptors at the periphery and GABAergic interneurons in the brain has analgesic and anti-inflammatory effects mediated by its sst4 receptor without involvement of endocrin functions [1]. Native somatostatin cannot be drug candidate due to its short elimination half-life and various endocrin effects. Sst4 receptor is highly expressed in pain-related brain regions and so can be a new target for drug development [2].
Aims: We investigated the effects of our novel small molecule sst4 receptor agonists in mouse models of neuropathic pain and acute neurogenic inflammation.
Methods: Sst4 receptor activation by our pyrrolo-py-

rimidine compounds was determined by the gamma-GTP-binding assay on sst4-expressing CHO cells. The effects of the two most potent and efficacious agonists were tested on partial sciatic nerve ligation-induced traumatic mononeuropathic hyperalgesia and resiniferatoxin (RTX)-induced thermal allodynia and mechanical hyperalgesia.

Results: Our novel compounds proved to be effective in G-protein assays and exert 60-70% maximal antihyperalgesic effects in the neuropathy model after a single oral administration of 500 μg/kg doses. In addition, one of the agonists is also effective analgesics in RTX-induced neurogenic inflammation model.

Conclusion: Our orally administered sst4 agonists are promising analgesic drug candidates for treating neuropathic pain.

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Instead of "I saw it on the internet, it must be true" – Patient education in the Cancer Center of Semmelweis University

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Background: Although greater and greater efforts were made to cure or at least treat long-term cancer, the society's reaction is very critical. It seems, that education programs can reduce the negative attitude of patients. For this, we have introduced weekly presentations in 2017.05.11 in the Cancer Centre of Semmelweis University, in conjunction with oncoteams. In the questionnaires we measured the reactions, but we have not checked how understandable is it. As the institute had to move because of the renovation of the building, we had a short break in the presentations, but started again in 2019.07.25 with few developments. In the past, a main pretence was a published document about the presentation, so an e-book has been published.

Aims: Our aim was to measure the reactions to the restarted presentations, with regard to the changes.

Methods: Simple survey was used, without harm of personal rights. The questionnaires have been made on the same day of the presentations from 25 July 2019 to 24 October 2019 Statistical analysis was made with Microsoft Office Excel 2016 (Redmond, WA).

Results: In this three-month period, the survey was filled by 53 people [mean age ± SD = 58 ± 13 (years)]. Most of the participants had cancerous disease and waiting for oncoteam (49%) or they were their relatives (43%). The remaining participants were waiting for treatment or consultation. We asked how beneficial the presentation was (answer type: fully useful/partially useful/partially useful, but mainly not beneficial/not useful). Most participants thought, it was fully useful (87%), while 13% thought it was partially useful. We asked, if it was understandable. Only one person thought it was just partially understandable, but mainly clear, all other thought, it was fully understandable. We asked what other topics the participants are interested in. Most of them (62%) highlighted the new biological treatments that may need a new presentation in the future.

Conclusion: All in all, our patient education program seems useful as no negative answer was in the survey. It is maybe the consequence of the plain language what most participants could understand and realize the significance of their role in the therapy.

Development of dermal semisolid dosage forms based on Quality by Design approach

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Background: Background: Semisolid dosage forms for dermal use receive more and more attention in the pharmaceutical and cosmetic fields. Semisolid systems are the most usual formulations for the delivery of drugs through the skin. Topically applied anesthetics are employed in order to eliminate the pain caused by needle insertion and injection, thus improving patient compliance. Due to fast market growth, a larger emphasis has been placed on proper planning of product development and on using modern tools such as the Quality by Design (QbD) concept. In such a way, the duration and costs of the development process can be reduced, while the requirements of the stakeholders, namely the patient, the industry and the regulatory authorities can be met more precisely.

Aims: The aim of our present work was to evaluate the applicability of Quality by Design (QbD) methodology in the development of semisolid dosage forms for dermal use.

Methods: The QbD concept involves identifying the quality target product profile (QTTP), the critical material attributes (CMAs) and the critical process parameters (CPPs) into the critical quality attributes (CQAs) of a drug product at the beginning of the development. The CQAs influencing the quality and efficacy of the final drug formulation were then defined in order to select the control points and proper

methods for measurements. The quality management tools (e.g. Ishikawa diagram, risk estimate matrix, Pareto analysis, etc.), Design of Experiments (DoE) techniques and the Design space are useful tools for QbD implementation. LeanQbD Software and StatSoft. Inc. Statistica for Windows were applied to identify the risks in the case of this study.
Results: The model systems were a Nanostructured Lipid Carrier (NLC) and a semisolid film-forming system preparation. The most critical CMAs and CPPs were chosen to be the independent variables and the CQAs were chosen to be the dependent variables in a 23 factorial design process. Based on our experiments, an optimal formulation can be obtained.
Conclusion: The risk assessment method is a helpful tool for the optimal product development process, allowing us to define the optimal semisolid formulation. Furthermore, the predefined aims (QTPP/CQA) is a powerful tool to guide the formulation and process design and to keep the product development effort focused and efficient.

Considering real-world data in regulatory decision making paves the way for innovation in clinical trials: the potential for using synthetic control arms in generating evidence

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Background: Randomized controlled trials (RCTs) have been the gold standard for measuring effectiveness of health technologies. Randomization provides a method for limiting systematic bias related to patient selection and treatment assignment. Although RCTs reduce the risk of bias compared to single arm trials, they tend to require large sample sizes, take longer to complete enrollment and actually patients have typically a lower propensity to enroll because of their fear of being put on a placebo arm. Recently, availability of data collected from electronic health records (EHR), prior clinical trials, lab tests, wearable devices and insurance claims has increased the interest in using real-world data (RWD) as a "synthetic" or "external" control arm in generating evidence.
Aims: The aim of this study was to describe the current regulatory environment of real-world data and derived real-world evidence (RWE) regarding their applicability and acceptance in healthcare decision making especially in comparative effectiveness studies.
Methods: Presented here is information summarized and interpreted from recently published guidelines of regulators, white papers and peer reviewed articles were found via a targeted literature review performed by our center. Here we present the basic definitions approved by regulators and the process and constraints applied during the development of fit for regulatory purpose RWE.
Results: The currently adopted definition of RWE reflects the fact that evidence generation is broader than passively-collected observational data and retrospective analytical approaches. Conceptually it allows prospective collection of wide variety of data and the use of study designs that are embedded in clinical practice but retain randomization. The applicability of RWE, which is suitable for specific regulatory purposes, depends on the study design to assess the effects of the treatment on the outcomes of interest, on the understanding of the context in which the treatments are used and on the transparency required during its development.
Conclusion: Although RWD are generally accepted as an adjunct to RCTs, more work must be done to clarify which types of RWD and derived RWE are robust enough to provide information on effectiveness, risk–benefit assessment and cost-effectiveness. For that purpose regulators have to clearly define key performance indicators of quality and conformity to support wide applicability of real-world evidence.

Encapsulation of human interferon-alpha (IFN- α) into core-shell nanoparticles

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Background: Nowadays, the administration route of IFN-α is frequent injection of the dissolved protein, because it is a very sensitive material. The frequent injections have disadvantages such as low patient compliance because of the pain they cause. One of the solutions can be the application of oral delivery of the IFN-α [1]. Patient compliance can also be increased with application of sustained release injection, for which the administration frequency is considerably lower. In a previous study bovine serum albumin (BSA) based core–shell NPs were developed as carrier systems for drug transportation [2].
Aims: The aim of our work is to achieve sustained IFN-α release after injection and test it in animal trials.
Methods: First step of the core-shell nanoparticle (NP) preparation was the precipitation of human serum albumin enriched in recombinant human

interferon-α (HSA-IFN-α) (Trigon Biotechnology Rt.) from its buffered solution with Na_2SO_4 solution. The resulting particles were separated by centrifuging. The second main step was the preparation of the polymer layers: poly(sodium-4-styrenesulphonate (PSS) and chitosan (Chit) (Sigma-Aldrich). The precipitated HSA-IFN-α was redispersed in the polyelectrolyte solutions followed by continuous stirring. Finally, the HSA-IFN-α core-shell NPs were lyophilized. The obtained HSA-IFN-α core-shell NPs were characterised with thermal analysis, zeta potential and dynamic light scattering measurement, X-ray diffraction, transmission electron microscopy, IFN-α activity test, dissolution study and in vivo study with rabbits.

Results: The new particle is formed by salt-precipitation of IFN-α containing HSA to 10nm sized particles and building up three polyelectrolyte layers on the particle surface in L-b-L strategy. The particle size is in the nano-size range, and that the outer surface is negatively charged were demonstrated. Encapsulation the precipitated protein renders it fully amorphous. IFN-α activity was not decreased. Both in vitro and in vivo release kinetics experiments have proven slow active agent dissolution from the formulation.

Conclusion: In this work a novel method of core-shell nanoparticle preparation for protein drugs or protein-bound active compounds was presented, which provides a relatively easy and inexpensive way of the formulation of sustained release products.

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Challenges and pharmacist aspects of health-economic assessment of computer provided order entry systems.

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Background: Mediaction errors (ME) and the consequent preventable adverse drug events (pADE) are a major burden to inpatient care. They not only cause patient harm but as a result of this prolonged length of stay (LOS) and increased healthcare cost. Computerized physician order entry (also known as computer provided order entry) with or without a clinical decision support tool (CDS) have been shown to increase patient safety. Due to the increasing burden on healthcare financing it is important to seek cost-effective solutions.

Aims: Our aim was to collect studies examining CPOE systems in inpatient care with cost or other resource utilization related outcomes, and to evaluate these studies from a methodological perspective, with special regard to full economic evaluations.

Methods: We conducted a systematic search of Scopus, PubMed and Web of Science database. Search terms were determined according to PICO. Non-english papers and studies providing no original data were excluded.

Results: Following a screening of 1693 abstracts, 67 full text articles were analyzed of which 27 met the inclusion criteria. We have identified 18 partial and 8 full economic evaluation. In this study we analyzed the full economic evaluations. The clinical outcomes are dominated by pADE, although LOS (1 case), QALY (1 case) are also apparent. The input parameters on the contrary are quite different. Each study has demonstrated cost-reducing and patient safety enhancing effect but differences are present in methods (perspective, discounting, duration, inflation, sensitivity, definition of ADE). Also most of the articles doesn't provide details about the level of CDS and if clinical pharmacist services were involved in the intervention.

Conclusion: Differences in methods and quality in health-economic analyses concerning CPOE are raising questions about the comparability of these studies. Currently in Hungary there's a good opportunity to analyze and compare CPOE systems due to the appearance of multiple Automated Drug Dispensing (ADD) systems in the country. Our results may help these studies from methodological perspective. In the following we will assess the type of CPOE, level of CDS and pharmacist interventions regarding Hungarian ADD systems.

In what is similar and in what is different? – Cariprazine, a new atypical antipsychotic

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Background: Dopamine D2 receptor partial agonists are representing a new generation of atypical antipsychotics. Cariprazine is one of the representatives of this group, which has received centralized market authorization from the European Medicines Agency in 2017 for the treatment of adult patients with schizophrenia including those with predominant negative symptoms of schizophrenia. Cariprazine is a dopamine D3 preferring D3/D2 receptor partial agonist with similar dopamine receptor subtype selectivity as the neurotransmitter dopamine.

Aims: Its short-term efficacy was proven in three phase 2/3 studies. The investigated doses were in the range of 1.5 to 9mg/day. Long term efficacy of cariprazine was proved in prevention of relapse after

26-96 weeks' treatment showing high separation from placebo both in the number of relapses and in time to relapse. In a head to head comparative study cariprazine showed significant improvement in the symptoms as well as in the everyday functions of predominant negative symptom patients of schizophrenia compared to the antipsychotic risperidone.
Methods: Cariprazine treatment generally was well tolerated by the patients and has a good safety profile. It doesn't cause prolactin elevation, QT prolongation, there is no remarkable and significant weight gain and there is no significant change in the metabolic parameters. Due to its pharmacokinetic properties once a day treatment with cariprazine is adequate and it doesn't cause significant food effect.
Results: Further phase-3 clinical studies proved the efficacy of cariprazine in acute treatment of manic or mixed episodes associated with bipolar I disorder, as well as in bipolar depression. For the adjunctive treatment of major depressive disorder, phase 3 studies are in progress.

Basic pharmacological characterization of EV-34, a new H_2S-releasing ibuprofen derivative

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Background: The cardioprotective effect of H_2S is being suggested by a handful number of manuscripts. Furthermore, H_2S plays a role in relaxation of vascular smooth muscle, protects against oxidative stress and modulates inflammation.
Aims: The goal of the present work is the synthesis and basic pharmacological characterization of a newly designed H_2S-releasing ibuprofen derivative.
Methods: After synthesis of EV-34 oxidative stability assays were performed (Fenton, porfirin assay). Furthermore, stability of the molecule was studied in rat serum. With the help of a hydrogen sulfide sensor H_2S-releasing ability of the molecule was studied in media originated from H9c2 cell culture. MTT assay was carried out to monitor the possible cytotoxic effect of the molecule. Cyclooxygenase (COX) inhibitory property of EV-34 was also evaluated. Finally, carrageenan assay was carried out to compare the anti-inflammatory effect of EV-34 to ibuprofen.
Results: Our experiments revealed that the molecule is stable under oxidative condition; however, in rat serum it undergoes biodegradation. In cell culture medium H_2S is being released from EV-34. No cytotoxic effect was observed at concentrations of 10, 100, 500μM. The COX-1 and COX-2 inhibitory effects of the molecule are comparable to those of ibuprofen. Furthermore, based on the carrageenan assay EV-34 exhibits an anti-inflammatory effect similar to that of equimolar amount of ibuprofen (100mg/bwkg).
Conclusion: Taken together our results suggest that the newly synthetized EV-34 is a nontoxic chemically stable compound, which release H_2S in biological systems. In addition, EV-34 has COX inhibitory and anti-inflammatory properties.

This study was supported by the GINOP-2.3.2-15-2016-00043 (IRONHEART), the Higher Education Institutional Excellence Program NKFIH-1150-6/2019 and EFOP-3.6.1-16-2016-00022 „Debrecen Venture Catapult" projects.

Quality Assurance Systems in Pharmaceutical Industry in the viewpoint of audits/inspections

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Dealing with the growing number of inspections/audits
– new countries starting to perform inspections (Russia)
Implications of MRA between US and EU (Is it possible to reduce the number of inspections?)
Possible optimization approaches
Tackling data integrity challenges and genotoxic impurity
Experiences of inspections

Machine vision as a multi-purpose PAT tool for continuous pharmaceutical manufacturing

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Background: Current manufacturing processes inherit several problems from process development, many of which can be prevented by shifting to continuous manufacturing processes. Some benefits of this shift include improved consistency (resulting in lowered scrap or recall costs), as well as better quality control- and manufacturing efficiency. With the installation of process monitoring tools, Process Analytical Technology (PAT) allows for real-time quality control. In addition, large amounts of data acquired during production can be used to further

enhance process understanding and efficiency. A process monitoring tool used extensively in many areas of the industry is computer vision, which could also prove useful in the pharmaceutical industry as well.
Aims: The aim of this work was to utilize computer vision for the in-line monitoring of different continuous pharmaceutical manufacturing processes (e.g. crystallization, tablet manufacturing). The real-time acquired data then can be used for quality control, process understanding or even process control.
Methods: A software was developed by the authors for rapid, real-time image analysis. A custom reactor was used for the continuous crystallization of Acetylsalicylic Acid, which allowed for real-time image analysis-based particle size analysis. Samples collected from the process were dried and analyzed via a Parsum IPP-70-S for reference particle size measurement. Tablets with different tableting compression forces were prepared for image analysis-based determination of tablet hardness.
Results: The developed image analysis software was successfully used to monitor the particle size distribution change during continuous crystallization, as well as to determine the steady state of the process. Tablet hardness was also successfully estimated from images via image analysis.
Conclusion: These solutions, when adopted by the pharmaceutical industry, can lead to well controlled technologies where the quality of the product is understood to a much deeper extent, and thus it can be assured that the patient will receive a treatment of the desired quality

The rough road to the first successful Hungarian gene therapy in Bethesda Children's Hospital of the Hungarian Reformed Church

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Background: Spinal Muscular Atrophy (SMA) is a fatal neurodegenerative disease which demands multidisciplinary care. SMA belongs to the class of orphan diseases, the occurance of the disease is 1:6000 among newborns, which means 12-15 new patients per year in Hungary. Before 2017 treatment did not exist for the disease. The first medicine – called Spinraza with active agent nusinersen – has been granted a marketing authorization in May 2017. In Hungary this therapy is funded to those children who are entitled to individual permission by the health insurance department. This treatment is available in two SMA centers: II. Children's Clinic of Semmelweis University and in Bethesda Children's Hospital of the Hungarian Reformed Church. The second milestone in the treatment was reached in 2019, when gene therapy called Zolgensma has been granted a marketing authorization by Food and Drug Administration (FDA) in the USA. The drug is not registered yet in Europe due to the few experience and the short time.
Aims: A child diagnosed with SMA was treated with Zolgensma in October 2019 first in Hungary, in Bethesda Children's Hospital of the Hungarian Reformed Church. The path leading to the treatment was not easy at all. I intend to present the professional background, the related challenges and the solutions.
Methods: I present the case study retrospectively about the treatment's circumstances that was used for the first time in Hungary and the fourth time in Europe. I expound the disease, the medicine in terms of effect mechanism, the process of getting the permission, the logistics and also the financial issues. I introduce the team who worked on this project and the cooperation within the hospital and with other institutes. This treatment required the development of a supportive therapy, which was implemented in collaboration with the pharmacists and the parents.
Results: After a month of careful organization, the therapy can be considered a scientific and professional success. After the therapy, the child is monitored.
Conclusion: Gene technology as a drug therapy can be seen as a paradigm shift in medicine that could open new paths for healing in the future. During the preparation of the treatment, the role of the multidisciplinary team in healing was confirmed.

Clinical decision making and pharmacist prescribing

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Background: Today's healthcare works within the framework of Evidence-Based Medicine, where scientific knowledge improves exponentially. Clinical decision making, therapeutic choices are made by teams, where one of the most important team members is the pharmacist. The pharmacist plays an essential role in health prevention as well as medication therapy management. Nowadays, in several countries, pharmacists have to face new challenges such as the complex activity of prescribing, this process started in England in 1999 within the framework of non-medical prescribing.

Aims: The presentation provides an overview of the actual experiences.
Methods: Expert's reports s and a literature review were performed between 2009-2018, in Medline with the following keywords: [non-medical or pharmacist] and prescribing with a limit to full text articles.
Results: Prescribing has three main aspects, prescribing as a discrete clinical activity, prescribing as a health professional activity, and prescribing as a policy process. It is a complex (with appropriate ethical and professional framework) evidence-based process, where one shall take patient preferences into account as well.
Non-medical prescribing, in the form of supplementary prescribing was suggested first for nurses by the first Crown Report (Review of Prescribing and Administration of Medicines (the Crown Report) Department of Health London 1989), the regulation came into power in 1992; supplementary prescribing meant that district nurses could prescribe limited number of drugs for certain conditions. This practice was developed further and was advised to be extended to pharmacist and optometrists in 1999 by the second Crown report (Crown J: Review of Prescribing, Supply and Administration of Medicines. Department of Health London 1999.) Supplementary prescribing for Pharmacist was made possible by the Department of Health in 2002. As this practice was successful nurses and pharmacist were enabled to become independent prescribers in 2009 (Medicines and Healthcare products Regulatory Agency 2009). Nurse and pharmacist prescribers today in the UK have the same prescribing rights as medical doctors.
Today the Health and Care Professions Council (HCPC) is the professional body who set the standards to carry out prescribing.
Conclusion: Clinical practice and various studies, such as Weeks et al, Courtenay et al 2017, Reid et al 2017 provide evidences that independent pharmacist prescribing is well functioning and is a safe activity both from the view of patient safety and health–service-provision safety; patients are aware, and they are very much accepting Pharmacist Prescribing as part of the GP practices.

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Historical review of drug packaging

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Adherence to dietary supplementations especially Calcium and Vitamin D as osteoporosis adjuvant therapy in comparison with prescribed medicines

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Background: A lack of compliance with the advised treatment regarding to every health situation is a common problem that may lead to worsening the medical condition or resulting in a lack of efficacy result. Recent studies have shown the use of calcium and vitamin D in the prevention and treatment of osteoporosis as dietary supplementation (DS) can play role as a general adjuvant therapeutic measure and a specific complement to the treatment with other active compounds.
Aims: To evaluate the possible factors influencing the patients' compliance through a „dietary intake specific questionnaire". To compare the patients' adherence to certain prescribed medications (Rx) rather than the DSs, also the patients' trust in the effectiveness of DSs and herbal medications. In the population who are consuming vitamins, to investigate their feeling of health improvement after a certain time period consuming it, which can be the patient motivation to continue and being adherent to the DSs.
Methods: A self-developed questionnaire was used. A database was compiled from the anonymous questionnaires filled in voluntarily by the patients. Basic statistics were used to analyse database.
Results: We received 477 responds. Gender ratio was 0.42 (139 [29.1%] male and 334 [70%] female). Good adherence to Rx was reported in 51 patients among male and 96 among female (OR: 1.44; 95% CI: 1.02-1.84, $p<0.0001$). 144 patients (30.2%) trust in vitamins and if necessary consume it, from them 96 patients (20.1%) take vitamin D. Out of 64 patients (13.4%) consuming continuously vitamin D, 39 (8.2%) take the same dose over the year and out of 91 patients (19.1%) taking periodically vitamin D, 30 (6.3%) take the same dose (OR: 3.2; 95% CI: 2.5-3.8, $p<0.0001$). Fifty-three patients (11.1%) take Rx and 50 patients (10.5%) are adherent among patients who take regularly vitamins. Seven patients (1.5%) are adherent to Rx out of 23 (4.8%) among vitamin non-consumers (OR: 38.1, 95% CI: 36.6-39.6; $p<0.0001$). Calcium supplementation (CaS) were used by 88 (18.4%) patients regularly, 30 (6.3%) patients frequently, 131 (27.5%) patients sometimes and 226 (47.4%) patients never. Among regular CaS users, 38 (8%) out of 82 (17.2%) patients adhere to their Rx and 44 (9.2%) out of 226

(47.4%) patients (OR: 3.57, 95% CI: 3.0-4.1; p<0.0001).
Conclusion: Adherence to Rx is significantly higher among male. Those patients who consume regularly vitamin D take the same dose during the year. Regular vitamin consumption and CaS enhance the adherence to Rx.

Actualities of quality assurance

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Luteinizing Hormon-Releasing Hormon (LHRH) receptor based new possible targeted therapy for human uveal melanoma

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Background: In the past decades, the average survival of patients has not changed in the case of uveal melanoma (UM). The average survival of metastatic patients with UM is less than one year, and despite the treatment of the primary tumor, metastases develop in more than half of the patients. The drawbacks of bad statistics are the rapid dissemination of the tumor cells but resistance to chemotherapy also plays a major role. Cytotoxic LHRH (luteinizing hormonereleasing hormone) analogs can be effectively used for targeting sexual hormone-dependent malignancies like endometrial, ovarian and prostatic cancers but the application of these analogs in hormone-independent cancers such as human uveal melanoma (UM) is not examined jet.
Aims: The aims of the current study were to investigate the expression of LHRH receptor and ligand in human UM tissues, as a potential novel therapeutic target. We also established a new in vitro model to study the cellular uptake and efficacy of cytotoxic LHRH analog AN-152 (AEZS-108, zoptarelin doxorubicin) in a doxorubicin-resistant UM cell line.
Methods: The expression of LHRH receptor and LHRH ligand was tested in 39 human UM specimens by RT-PCR with specific primer set for full length LHRH receptor. Radio ligand binding characteristics of LHRH receptors were studied in tumor membranes of ten UM specimen. The presence of LHRH receptor protein has been confirmed by immunohistochemistry. We established a new doxorubicin (DOX) resistant UM cell line by stepwise administration of DOX to OCM3 human UM cells. The LHRH receptor expression of DOX sensitive (OCM3) and DOX resistant (OCM-3DOX320) UM cell lines was determined by exon specific RT-PCR and the immunocytochemistry. Cellular uptake and intracellular distribution of DOX and AN-152 were imaged with confocal laser scanning microscopy. Comparative cytotoxic activity of DOX and AN-152 were tested on both cell line by MTT assay.
Results: High percentage (46%) of UM specimens expressed the mRNS of full length type 1 LHRH receptor and 69% of samples were positive to LHRH ligand expression. 70% of the tissue samples showed high ligand binding affinity to LHRH receptors. Immunohistochemistry also confirmed the presence of LHRH receptors. We were able to establish a new DOX resistant UM cell line. Our study demonstrated the expression of LHRH receptor splice variants and protein isoforms in OCM3 and OCM3DOX320 cell lines. The cellular uptake of AN-152 was confirmed by fluorescent microscopy.
Conclusion: Based on the MTT assay AN-152 effectively inhibited cell proliferatin in both cell line in dose dependent manner. Our results demonstrated that LHRH receptors and its isoforms can be potential molecular targets for an effective targeted therapy of UM and its metastases.
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Clinical studies at the University of Debrecen

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The Coordination Centre for Drug Development was established in 2013 to serve as an independent organisation under the guidance of the Rector and Chancellor. After the Senate approved our bylaws of operation, we launched our unit, setup our website, instituted ways of supporting electronic file processing, and followed a single contract model.
Our primary goal was to speed up administrative processes, improve communication with sponsors and CROs, ultimately increasing the number and intensity of trials. We also defined our ambitions to become leaders in the field as well as collaborating intensively in the international arena.
A new strategy in communication was developed, sharing more information about clinical studies and highlighting the advantages of the University of Debrecen, concerning both human resources and infrastructure. We achieved prime partnerships not only with sponsors and CROs but also with general practitioners as well as patients and relatives.
As a result of efforts, during the last five years we more than doubled the number of contracts and tripled the revenue. Recent focus includes improving the quality of our services. Lately we have developed a web-based quality assurance system for all clinical studies run at University level where we record

studies, analyse data, and provide feedback on progress to principal investigators and the University management in a quarterly report.

Losses suffered by the Hungarian pharmacy due to the borders defined by the Treaty of Trianon

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We must remember an event took place 100 years ago. The consequences of the border adjustments resulting from Trianon have affected the whole country's pharmaceutical network. Transylvania, Máramaros, Partium and East-Bánság have been attached to Romania, thus Hungary lost 102.813km^2. From these areas 1,662.000 people (according to population census in 1910), 31.78% of the total population have come under Romanian authority. The Hungarian pharmacy in 327 towns have lost 477 pharmacies. Later, in the detached towns more pharmacy owners, employees have migrated, so more pharmacies have ceased. As a replacement, the Romanian authority have given 174 new pharmacy rights, this way in the detached areas 65.5% of the pharmacies got into Romanian hands. In an issue, called Gyógyszerészek zsebnaptára (Pocket calendar of pharmacists), published in Budapest, 1918, the pharmacists from Transylvania are included, their pharmacies are mentioned, so does the town where they operated. In later years, the published almanachs (pocket calendars) have no longer reported these data. This way for a period of time the pharmacists from Transylvania were isolated, they could hardly make contact with each other. Jenő Nagy (1891-1980), young pharmacist in his early thirties from Marosvásárhely undertook the task to organize collecting data, then he edited the data his collegues have sent to him and finally, at his own expense, he published the issue named Gyógyszerészek címtára és zsebnaptára (Pocket calendar and directory of pharmacists) for the year 1921, I. period. He stopped collecting data 15th, December, 1920. Publishing data of pharmacists and pharmacies from Transylvania and Bánság have helped making contact with each other for those pharmacists who stayed in Hungary. A tradition has been created, because after this, similar issues, calendars, directories, year books (almanachs) were published regularly, every year or second year, up until 1937.

GMP audits and inspections; similarities and differences

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GMP audits and inspections are important events for both parties, regardless of which side you stand. They are assessments of the auditee's/inspectee's systems and can play a critical role in the approval or the image of the companies; ultimately they can have a huge impact on market supply to the patients who need to receive pharmaceutical products of the highest quality. This is our mutual interest and mission.

Both audits and inspections are well-defined processes and certain standards are used but the way they are approached, communicated, executed, and followed-up might vary significantly. These aspects, including how the observations are formulated and reported mainly depend on the inspectors/auditors and where the agency/company is from, as well as on the staff of the company that is inspected/audited. The lecture aims to give insight to audits, inspections and self-inspections with respect to how different they could be and what impact they might ultimately have on the companies' compliance level. It is not attempted, to give a „study book" type picture but rather an experience-based personal (but objective) review of these assessments.

Over-the-Counter pain relief: actualities and the role of the pharmacists in the field of self-healing and self-medication

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Background: Pain is more than a feeling of discomfort. Depending on the intensity of pain it can affect the quality of everyday life. It may also lead to mental health conditions like depression and anxiety. The amount of pain can influence the overall health. Pain is the most common symptom in the musculoskeletal diseases. People can experience pain as an acute, chronic, or intermittent condition, or a combination of the three. Specifically, chronic pain is a complex condition embracing physical, social and psychological factors, leading to disability and poor quality of life. It seems to be important to support pain relief in a way that is accessible to all. Pain-relief methods range from at-home treatments and prescriptions to over-the-counter (OTC) medications and invasive procedures like surgery. Each person's pain experience is unique to them. A wide variety of painkillers is offered, analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) are available. This greatly facilitates the patient or many times the doctor's job as well. The future offers an even wider range of over-the-counter drugs, with the possibility of more frequent combinations and side effects. How do we take advantage of this opportunity? How can we save time by not waiting for a medical examination?

Discussion: Among the principles of pain relief, it is important to follow the steps of pharmacological pain relief and consider invasiveness. It is suggested to seize the opportunities of non-medical and percutaneous methods. Both analgesics and NSAIDs reduce fever and relieve pain caused by muscle aches and stiffness, but only NSAIDs can also reduce inflammation. Paracetamol, metamizole and NSAIDs also work differently. Non-opioid painkillers are the most common type of painkiller. Paracetamol is available over the counter and it is often the first treatment for mild to moderate pain. NSAIDs work by inhibiting the activity of cyclooxygenase enzymes (COX-1 or COX-2). In cells, these enzymes are involved in the synthesis of key mediators (prostaglandins), which are involved in inflammation, and thromboxanes, which are involved in blood clotting. Most NSAIDs are non-selective and inhibit the activity of both COX-1 and COX-2. These NSAIDs, while reducing inflammation, also inhibit platelet aggregation and increase the risk of gastrointestinal ulceration. COX-2 selective inhibitors have less gastrointestinal side effects but promote thrombosis and substantially increase the cardio- and cerebrovascular risk, especially in elderly people.
Conclusion: Pain reduction is a professional and social expectation. A wide range of methods is available, yet it is often not an easy task. Especially in the case of elderly people we should count with multiorgan failure and comorbidities, so the individual medication and the adaptation of the side effects profile is essential. In conclusion, due to the importance of the OTC medications the role of the pharmacists is crucial.

Interactions of flavonoid metabolites with serum albumin and biotransformation enzymes

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Background: Flavonoids are contained by several foods, dietary supplements, and medications. Flavonoids have poor oral bioavailability, therefore, mainly their metabolites appear in the blood and in other tissues. During the first-pass metabolism of flavonoids, conjugated metabolites are formed in enterocytes and/or in hepatocytes. As a result of the high intake of flavonoids (e.g., through the consumption of dietary supplements), their significant concentrations appear in the colon. The colon microbiota can also biotransform flavonoids, during which small phenolic fragments are formed. Microbial metabolites may also be absorbed. The pharmacokinetic interactions of flavonoid aglycones have been widely studied; however, only limited information is available regarding their metabolites.
Aims: In these studies, we aimed to investigate the interactions of conjugated and microbial flavonoid metabolites with serum albumin and biotransformation enzymes.
Methods: Flavonoid-albumin interactions were examined with fluorescence spectroscopy and ultrafiltration. The in vitro enzyme inhibition assays regarding cytochrome P450 (CYP) and xanthine oxidase (XO) were performed with CypExpress kits and with the pure enzyme, respectively.
Results: Methyl, sulfate, and glucuronide metabolites of quercetin and chrysin as well as 24 microbial flavonoid metabolites were examined. Quercetin-3'-sulfate and chrysin-7-sulfate formed more stable complexes with albumin and showed higher displacing ability than the parent compounds. Some conjugates significantly inhibited CYP2C19 and CYP3A4 enzymes. Sulfate and methyl metabolites showed similar or even higher inhibitory effects on CYP2C9 enzyme compared to the flavonoid aglycones. XO enzyme was strongly inhibited by the sulfate and methyl conjugates of quercetin. Some microbial metabolites (e.g., pyrogallol, desmethylangolensin, and 2,4-dihydroxyacetophenone) were also able to interact with albumin and/or biotransformation enzymes.
Conclusion: Based on our observations, it is reasonable to hypothesize that flavonoid aglycones and some of their conjugated or microbial metabolites may cause the development of pharmacokinetic interactions. Therefore, the simultaneous administration of high-dose flavonoid-containing dietary supplements with drugs need to be carefully considered.

Mucoadhesive films as innovation products.

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Background: This presentation is based on the literature reviews of the benefits of mucoadhesive drug delivery systems, mechanisms involved in mucoadhesion and different factors affecting mucoadhesive drug delivery systems.
Aims: Although the oral route is the most popular way of administration of medicines for patients, the enzymes of the gastrointestinal tract decompose many active substances and the first-pass effect decreases the serum level of active pharmaceutical ingredients, too. Mucoadhesive films are not only local, they can also cause systemic effects, and even special substances such as small molecule proteins can be used. Oral mucoadhesive films are welcome

in paediatrics, but the films are also appropriate for elderly patients who suffer from swallowing disorders.

Results: The author wishes to illustrate with examples from the literature the direction of the research of bioadhesive films, what difficulties are encountered in formulation, which are the critical factors in the preparation of a pharmaceutical formulation. It is very important to understand the different mechanisms involved in mucoadhesion to formulate an optimal dosage form. The first important factor is the choice of the suitable film-forming polymer, for which a variety of chemically structured polymers may be adequate. Of course, it is almost mandatory to use a plasticizer in the composition to make the films elastic, so the type and amount of the plasticizer is a very important parameter. The author would also like to give an overview of the active substances that can be found in the literature of the research of this pharmaceutical form. The testing methods for film rating will also be presented, with particular regard to adhesion property, tensile strength, other physico-chemical properties and, of course, the dissolution test.

Conclusion: By presenting examples from the literature, the author points out that bioadhesive films as pharmaceutical forms provide a relatively new innovative route to therapy that requires appropriate drug formulation.

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Unit-dose or ward-based medication management, what does the statistics teach us?

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Background: Our institute declared patient safety as high priority and since the number of medication errors are a good indicator of that, we introduced a new method to try and reduce them. Damages caused by the health sector are a heavy burden to bear by society. Consequently if we invest in patients' safety that would bring obvious benefits to them, and might even reduce our costs.

Aims: Our goal is to compare the types and rate of medication errors occurring at conventional, ward based medication prepared by nurses versus centralized medication supported by automation and clinical pharmacists in the hope that the latter means significantly fewer errors. Additionally we investigate the specific indexes of given wards during both periods such as drug costs per one nursing day/case/weighting factor to see how the new method affects these numbers. Our overall goal is to prove the great usefulness of the new method looking at different aspects.

Methods: Quantitative research at Mining Rehabilitation and Night Time Sanatorium, Health Centre of Komló; internal medicine, chronic internal medicine and nursing departments; 2017 August and 2020 February. On two given days we inspect all the medicines prepared by the nurses or the hospital pharmacy, comparing the written orders and the drugs dispensed (involving the patient's own drugs), at the second date even comparing the written orders and the ones recorded in the medical software. We excluded parenteral medications from our investigation. The target group involves all the patients above the age of 18 from the three wards mentioned before. We do not investigate interactions or the effects on the patients caused by medication errors. We used different kinds of descriptive statistical methods to evaluate our results.

Results: The ward that provided medications for a 24 hour period operated with a 15% error rate, the other two that prepared medications weekly had a 30-50% error rate when the nurses prepared the medications manually from the written instructions. These both came down to a less than 2% error rate with the newly introduced unit-dose system. Besides this the drug costs dropped at the chronic wards by 18% percent just after the first 6 months of using the new method.

Conclusion: Our research verifies that using the unit dose medication system significantly reduces medication errors and drug costs in the specific indexes. Therefore we are more able to ensure patient safety in our hospital followed by reduced drug costs and optimized medication utilization.

Formulation and evaluation of herbal drug preparation for the prevention and treatment of insulin resistance

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Background: Insulin resistance is a major global health issue of the 21st century, an estimated 33.9% of the U.S. adult population had prediabetes in 2017. It is seen as the threshold of the type 2 diabetes. Insulin resistance can lead to obesity, heart disease, or polycystic ovary syndrome. The treatment of the condition is based on lifestyle changes, including proper, low-carbohydrate diet, physical activity and weight loss. Botanical extracts have been widely used throughout history as medicinal agents for improving metabolism or treating diabetes. There are

scientific investigations of herbal agents used to treat or reverse insulin resistance. The botanical extracts can assure an effective, commonly available and cheap therapy, with a generally higher patient compliance toward it than synthetic drugs.
Aims: In our work, we developed a product taking advantage of the combined effect of fenugreek and pepper.
Methods: We carried out citotoxicity assays of the botanical extracts, transport tests on CaCo-2 human adenocarcinoma cells, and modified dissolution tests to evaluate the product.
Results: Our research proved the safety and the increased bioavailability of the product.
Conclusion: We successfully developed a herbal drug delivery system with increased bioavailability, stability, and sustained API release.

Using Flux Measurements for Prediction of Bioequivalence of Drug Products of Poorly Soluble Compounds

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Background: For generic formulation development traditional (USP) dissolution tests have been used in the pharmaceutical industry to compare the performance of different drug formulations before conducting bioequivalent studies. Although dissolution tests provide a simple way of testing formulations, the in vivo predictive power of these tests is not always satisfactory.
Aims: The aim of this study was to represent how simultaneous dissolution-absorption studies can provide more complex information on brand and generic formulations.
Methods: μFLUX™, BioFluxTM and MacroFLUX™ instruments (Pion Inc) were utilized to compare the behavior of brand and generic formulations. Examples of itraconazole and telmisartan formulations are presented. Assay parameters were aiming to mimic the in vivo conditions.
Results: The dissolution and flux results of three marketed itraconazole and five marketed telmisartan formulations were compared in fasted and fed state to each other and to the in vivo study results published in the public assessment reports. The differences of itraconazole formulations in in vivo human fraction absorbed data were possible to be captured by the in vitro studies reasonably well, especially considering the significant deviation in dissolution kinetics due to the differences in composition and formulation strategy. Telmisartan formulations provided more similar dissolution behavior that made it possible to correlate in vivo deviations to in vitro flux results.
Conclusion: The in vitro test was found to be successful in predicting dissimilarities among formulations caused by different excipients and formulation strategies and produce the same rank order of formulations in fasted and fed state as in vivo results do. Although the applied in vitro models are not able to simulate all aspects of human absorption, they appear to be a useful tool in formulations comparison and in absorption estimation.

Comprehensive, patients' adherence development program in Hungarian community pharmacies The first results of the pilot period

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Background: The aim of the adherence development projects is to make a patient a real partner in the therapy following the advices of doctors and pharmacists.
Aims: "My Medicines 5xM" pilot program was started in October 2018 as the introductory phase of a comprehensive, adherence development program in the Hungarian community pharmacies. One of the main objectives was to attention to the importance of correct use of medicines.
Methods: A printed leaflet for patients was compiled to focus on the correct, general application rules. It included a short questionnaire in which patients evaluated the usefulness of the text. The leaflets were delivered to 208 pharmacies and a self-developed pharmaceutical guideline was available to them, printed and online (detailed version). In March 2019, feedback was collected from pharmacies and participating professionals.
Results: The patients' questionnaires were collected from 80 pharmacies with 1082 participants. The leaflet helped 91 percent of patients to ask their questions more freely in the pharmacies. After reading, 90 percent of respondents are more aware of information about their medicines. 510 patients changed their incorrect medicines application habits. The text also included new information for 52 percent of participants (e.g. drug-food interactions in 92 cases).
In the electronic, feedback questionnaire survey participated 205 pharmacies. Based on this, 136 pharmacies found the leaflet useful and 40 pharmacies found it very useful. According to the most pharma-

cies (84 responses), the pilot program helped them mostly to increase the therapeutic support of their already known patients, but several pharmacies managed to create a more "patient-friendly" atmosphere (53 pharmacies). The communication section of the pharmaceutical guideline was utilized by the most pharmacies, but tables summarizing interactions were also frequently used.
Pharmacists and assistants responded to the online, feedback questionnaire survey (76 persons). The importance of the program was rated as mean score 4.3 on a five-point scale. The leaflet was considered very necessary by 39 respondents (mean score 4.25). The guideline was found important by 34 professionals, but not very important. The workshops of the program were considered clearly useful.
Conclusion: This program is currently taking place in all Hungarian community pharmacies. In addition, the improved, general pharmaceutical methodology (guideline), other therapy specific guidelines and leaflets have been published.

Role of clinical pharmacists in the risk assessment of healthcare associated infections (hai) in a surgical unit

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Background: The nosocomial infection rate in patients in a facility is an indicator of quality and safety of care. The development of risk assessment process to monitor this rate is an essential first step to identify local problems and priorities, and evaluate the effectiveness of infection control activity. Risk assessment by itself, is an effective process to decrease the frequency of hospital-acquired infections.
Aims: The ultimate aim is the reduction of nosocomial infections, antibiotics and proton pump inhibitors (PPI) overuse. Doctors, clinical pharmacists and hospital hygiene service must work cooperatively to reduce the risk of infection.
Methods: The annexes 2. and 3. of the decree have been adapted to eMedsol computer system. The risk assessment forms are completed by clinical pharmacists. The completed data sheets are displayed in the eMedsol system as a part of the patient's examinations, e.g.: blood tests. The data sheets have to be filled out again as a new risk factor appears, e.g. after operation, catheter placement or intensive care. The risk assessment forms were filled over an 8-week period, from 9 September to 8 November 2019 at the Department of Vascular Surgery.
Results: We have completed the risk assessment for 109 patients. 51 patients were in high and 38 patients were at medium risk for nosocomial infections. 48 patients were in medium and 41 patients were at high risk for multiresistant microbial infections. Most of the patients were elderly (> 65 years old), and have more comorbidities, such as diabetes or obesity. Furthermore, in their anamnesis they had hospitalization within the past year, which contributes to the high risk of nosocomial infections.
Conclusion: Overuse of antibiotics and PPI could be responsible for the high risk of multiresistant microbial infections. In both cases, inappropriate and prolonged use of devices, such as CVCs, urinary catheters, which are also monitored by the questionnaires, may cause high risk. We also aimed to include more surgical departments into our risk assessment, and together with our clinical pharmacist colleagues implement it to several clinics. These questionnaires help us to reduce antibiotics and PPI overuse.

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József Antall and the history of pharmacy

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He started to teach in 1955, as a Hungarian literature and history teacher. He graduated from Eötvös Loránd University, Faculty of Humanities. However, because of his political actions, he was permanently banned from teaching, that's how he became a librarian. In the autumn of 1963 he was a scientific colleague in the reorganized Semmelweis Medicinal History Musem, from 1964 he was a senior fellow, over time deputy director, from 1974 appointed director, from 1985 director-general. An unexpected publication request made him well known in scientific circules. He recognized in these times how important it is to know medical history and how unprocessed it was. He determined, that medical and pharmaceutical history is basically a „musem science", because all the relevant data and material can only be found in museums. Enormous tasks awaited him, as a historian. He already has pointed it out in the basic draft, that the Musem and the Library needed to be united. He took on a prominent role in organizing Semmelweis Medicinal History Museum, Library and Archives. He made this institution internationally acknowledged. He noted the needs of Health Care System, elaborated guidelines according to it and the Ministry of Education have approved it under the number 67144/67. This new insti-

tution has become the center of Hungarian medical and pharmaceutical history. The relevance of the institution has truly shown, when József Antall achived that professional history has become a subject in the faculty of medicine and pharmacy in the mid-1980s.

He won the election as the president of MDF party in 1990, thus he could found the government. In spite of his serious illnes, he was the prime minister until 12th december, 1993. As a religious man, he lived his life according to his faith. Just like any other Hungarian politician in the era of enlightment, he had a stiff character, he was well-prepared, classy, he politicised, when he needed to, but he created something everlasting in the area of scientific life.

Synthesis, chemical and biological application of steviol- and isosteviol-based diterpenoids, obtained from *Stevia rebaudiana L.*

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Background: In the recent decade stevia glycosides (isolated from Paraguayan shrub *Stevia rebaudiana L.*), have been proved important natural compounds in the market of artificial sweeteners because of the easy cultivation, the high diterpene glycoside content of the plant, and easy isolation of its glycoside content. Because of the huge volume isolation of glycosides, the aglycon steviol and its isomer isosteviol have come into prominence nowadays as promissing starting material for the synthesis of bioactive compounds.
Aims: The aim of the present lecture is to give a short review on the chemical and biological applications of this promising diterpenoid type compounds according to the literature and our recent results in this field.
Methods: Stevia glycosides have complex diterpenoid glycoside molecules comprised of an aglycone, steviol with the ent-kaurane skeleton and three or four molecules of glucose or other monosaccharides. Hydrolyzed under alkaline or acidic condition, they generate ent-kaurane diterpenoid steviol or ent-beyerane diterpenoid isosteviol. Except for direct applications, they are widely used to provide ent-kaurane or ent-beyerane core structures for further medicinal chemistry study.
Results: Since of its industrial volume preparation, steviol have been proved excellent starting material for the synthesis of ent-kaurane diterpenoids with wide range of biological activity such as cytotoxic and apopthosis, or glutathione S-transferase inducing activity. Some, at C4 position COOH→NH_2 substituted derivatives possess inhibitory effects against *Hepatitis B virus*. In the recent years several reviews have deeply discussed syntheses of steviol based polyols, or even more complex structures. Isosteviol derivatives prepared with wide range of chemical modification also have proven interest molecules with remarkable pharmacological activities. Some poliol type isosteviol derivatives bear antiproliferative activities, evaluated against human gastric carcinoma MGC-803, HepG-2 and breast carcinoma MDA-MB-231 cell lines. Similarly, excellent antiproliferative activity was observed on the wide range of human cancer cell lines by some structural modifications done at the C-19 of beyerane-skeleton of isosteviol. Some, at C4 modified isosteviol analogues showed suppressing activity against the *Hepatitis B virus* too.
Conclusion: In summary it can be concluded that steviol and isosteviol are excellent starting materials for the development of pharmacologically active diterpenoids, as new drug candidates.

Presentation of our Pharmacy History Collection – past and heritage provide future!

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Background: Nowadays modern expressions like marketing, customers' habits, customers' joy and experience can be also detected regarding pharmacy, new segments in pharmaceutical sciences.
Who knows, whether only new and fascinating trends can be atrractive to the New Age People, or we can trust in classical, well-known and traditional things, as well?

During this 21st century the progress of new technologies, including medical and pharmaceutical sciences is enormous and revolutionary; although past and history seem also essential to remain in focus.

Luckily, in the territory of the former Hungarian Kingdom many traces of old pharmacies and pharmaceutical history can be detected, and those communities are really proud of such mementos, memories.

The most precious ones are considered as real museums with all the connecting prestige: they are pharmacy museums.

There are also collections, and in some cases museum pharmacies can be seen „in everyday work", equipped with precious old pharmacy-furnitures.

At the beginning of the 1990s, in our hometown, Karcag a collection of old medicine and pharmacy history was established and owned by the Town Council; although its operation seemed to be difficult and loaded with many problems. Visitors often encountered difficulties when they wanted to see the reliques.

Aims: Our aim was to establish a pharmacy history collection – as part of our pharmacy; which can be visited parallel with the opening hours of the pharmacy and to enhance the prestige of pharmacy and pharmaceutical sciences int he local community.
We aimed to target those patients and customers who might tend to be susceptible regarding history and pharmacy.
Methods: Beside the establishment of this collection, we do not consider it as „finished" work; we are waiting for further new pharmacy reliques offered in the future.
Results: In 2019, our family-owned pharmacy named „Betania" could have been given place for a pharmacy history collection, where old pharmacy furnitures donated by Karcag Town Council and old family reliques, books can be seen. We are proud of the fact that our Family can be considered as pharmacist dinasty, as from the 18th century there were known pharmacist members among our ancestors.
The room serving as place for the collection used to be the former „officina" of the Betania Pharmacy, and these special values can be seen continously through a special, glazed door.
In case visitors want to look around more precisely among the items of he collection, visit can be organized by us.
Conclusions: Up to our very fresh" experiences, the local community seems to be amazed and interested in historical things; some of our patients have already donated few items for the private collection.
Among our aims, we would like to organize minisymposiums dealing with health sciences, and schools are also warmly welcomed in the future.

We hope, the young generations might get inspiration to choose pharmacy and pharmacist profession.

We would like to inspire our Colleagues – in case proper circumstances are given – to establish such collections for the joy of the local communities.

Targeted delivery of essential oils for pharmaceutical applications

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Background: The medical use of essential oils (EOs) is well known from the traditional medicine, but modern pharmaceutical applications of EOs are made difficult because of the unfavourable physical-chemical properties of EOs, such as hydrophobicity and low water solubility. The traditional method to enhance solubility of EOs is application of their solution, usually ethanolic, or to enhance their solubility with the application of surfactants. Nanotechnology has several successful methods to enhance solubility of poorly water-soluble drugs that has been rarely used to increase the solubility of EOs or to provide targeted delivery of active ingredient from EO to treatment site.
Aims: We aimed to find alternative pharmaceutical applications of essential oils, define the specific targets, and design the delivery form for EO to specific treatment target. We have found several applications where EOs have a proven pharmaceutical activity, like treatment of nail infections, in mouth care or to test general antimicrobial activity of EO. We have chosen to formulate Pickering nanoemulsions with EOs and compare their effectiveness with conventional formulations.
Methods: We have classified EOs regarding their physical-chemical properties. The properties of Pickering emulsions have been defined based on the specific target, mainly considered the size of the emulsion droplets, surface properties of stabilising nanoparticles. For each of the applications, we have optimised the production method for Pickering emulsions to reach the desired properties. The nano formulated EOs have been tested for their effectiveness in antimicrobial tests and in vitro model tests. The toxicological concern regarding nanoformulation has been considered, and several tests have been made to examine the toxical effect of nanoformulation.
Results: We have published our results in several scientific papers, some of the results will be presented in the conference lecture.
Conclusion: We have found that targeted drug delivery can be achieved with nanotechnological formulation. In our research, we have found that Pickering emulsions formulated for a specific target, is more effective than conventional formulations. It has been found that applied nanoparticles have no toxic effect; the toxic concentration of nanoparticles is magnitudes higher then they have been applied in formulations of Pickering emulsions.

Imapct of patient education programs among adolescents

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Background: Adverse effects of medical treatment resulted in 142,000 deaths in 2013 up from 94,000 deaths in 1990 globally. (1) The development of side effects can be a consequence of incorrect medication.

We believe that with a proper patient education, we could prevent several side effects in some cases. At the age of 14, people are allowed to buy their own medicines, meanwhile they possibly don't understand the patient information package leaflet.
Aims: Our aim was to evaluate the 14-18 y.o. children's health status, the level of knowledge about the safe use of medications; the impact of demand within the framework of the national educational system of health-education and wheter the pharmaceutical care provided by pharmacists can be possibly in support for this age.
Methods: We prepared a survey and evaluated 1021 responses with Microsoft Office Excel 2013 program. Within a pilot study an interactive classroom presentation was hold. Shortly after a second questionnaire was distributed to evaluate the impact of information they perceived. Based on results, we established a scholarship among pharmacy students to educate children in schools.
Results: 24% of students take regular medication. 84% of them were ever used medicines as self-medication, 21% never been in a pharmacy, 45% never heard about pharmaceutical care. 10% use webshops to buy OTC medicines and/or dietary supplements. The pilot and following presentations was proved to be successful by feedback: 100% of respondents heard new, useful information, 80% of would take part in similar lecture, 60% prefer to contact a pharmacist for advice for the future.
Conclusion: The proper use of medications has a great impact in aspects of pharmacovigilance. Better knowledge of health and medication-related question among young people achieved by the increase of confidence towards pharmacists in pharmaceutical care would enhance the next generation in safer drug use and health-conscious life to live.

Development of health literacy-promoting communication in Hungarian community pharmacies, investigated in general patients and in a group of patients with type 2 diabetes mellitus

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Background: Health literacy is „the degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decision." More than half of the Hungarian population has low levels of health literacy. Community pharmacists have a key role in providing patients with adequate and reliable information about their illness and medicines, but it is crucial that the information is consistent with the level of their health literacy.
Aims: The aim of our research was to develop a communication model system in Hungarian community pharmacies that supports health literacy, including a drug dispensing process to the patients that improves their health literacy, and to examine the applicability of the developed methodology in pharmacy practice.
Methods: The research was conducted by pharmacists and pharmacy assistants. The study involved a general patient group and a special group of patients with Type 2 Diabetes (T2D). At the beginning of the project, we conducted self-developed questionnaire surveys of patients' and staff's opinion about the health literacy-friendly practice in their pharmacies, then the employees received a special pharmacy communication training (three-step postgraduate training). Three months later, we repeated the questionnaire with staff, the same T2D patients and other general patients. We conducted a descriptive and deep statistical analysis of the questionnaires.
Results: The study included 333 professionals from 69 pharmacies, 890 (at the beginning) and 847 (at the end) participants from the general patient group and 815 participants from the T2D group. In the general patient group, the mean result of the first questionnaire was 64.19%, which increased to 72.78% by the end of the project ($p<0.001$). In the T2D group, the mean result of the first questionnaire was 57.87%, the mean result of the second questionnaire was 74.73% ($p<0.001$). For professionals, the mean result of the initial questionnaire was 74.68% which increased significantly to 85.20% ($p<0.001$).
Conclusion: All in all, it can be stated that the targeted communication training of the pharmacy staff and the new communication practice in the pharmacies have a positive effect on all patients, whether they are patients with special needs (T2D) or general patients. Based on these results, there is a particular need for the widespread implementation of these developments in Hungary.

Post-splenectomy vaccine prophylaxis in the Department of Surgery

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Background: Infections caused by Streptococcus pneumoniae (pneumococcus) continue to be a serious problem in both the paediatric and adult populations, causing not only high morbidity but also high mortality rates. The most common and there-

fore probably, the most important adult pneumococcal disease is pneumonia. Patients with splenectomy due to splenic rupture have an increased risk of serious infections caused by pneumococcal disease. Therefore, pneumococcal vaccination is recommended for all patients with anatomical or functional asplenia, which should be given to the patient 2 weeks prior to the planned surgery or 7 to 10 days after the accidental splenectomy. Two types of vaccine are available for active immunization, Prevenar 13 suspension for injection and Pneumovax 23 solution for injection.

Aims: Our aim was to arrange the proper vaccination of patients who have undergone surgery in the Bajcsy Hospital, Department of Surgery. Occasionally, they did not follow the guidelines and the patient was not adequately vaccinated.

Methods: Within the framework of clinical pharmacy, I supervised the prophylactic antibiotic treatment for splenectomized patients, participated in the procurement of vaccines, and made policy choices.

Results: Between January 2, 2019 and July 31, 2019 I have followed the vaccination of 5 surgical patients against pneumococci. Patients received prophylactic antibiotic therapy (2x250 mg Amoxicillin or 2x250 mg Clarithromycin) prior to vaccination. Their final report showed exactly when they received the vaccine. If they have not been vaccinated, when will pneumococcal vaccines be given, all of which will provide the general practitioner assistance and information.

Conclusion: As a clinical pharmacist I have overseen splenectomized patients in order to prevent pneumococcal disease, from antibiotic prophylaxis to vaccination to the new guidelines, thus helping the work of the department and increasing patient safety.

Persistence of biologic treatmens in patients with inflammatory bowel disease

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Background: Biological drugs are known to be effective for treating inflammatory bowel disease (IBD). However, therapy discontinuation still appears frequently reported by many studies for various reasons. High cost of medication, sideeffects and loss of response can be identified as reasons. for quitting therapy.

Aims: To evaluate the persistence of biologic treatments in patients with IBD and to compare the results with reports from other countries.

Methods: In this single center, retrospective study using administrative claims database of the Hungarian National Health Insurance Fund, patients receiving adalimumab, infliximab, vedolizumab or ustekinumab therapy between 2017 and 2019 were included. Demographic characteristics, therapy discontinuation and switch were analyzed.

Results: Overall, 133 people with IBD were prescribed biological therapy during the two-year timespan, 57 infliximab, 62 adalimumab, 9 vedolizumab and 5 ustekinumab. Biological treatment was switched in 21 cases and only 11 people discontinued the medication completely, all of them were from the Anti-TNF Inhibitor group. 3 out of 11 stopped using infliximab and 8 out of 11 discontinued adalimumab therapy.

Conclusion: 8% (11 of 133) of the patients discontinued the biological therapy for various reasons (2 remissions, 2 bowel resection, 2 no response, 2 patient complience, 1 cancer, 1 adverse drug reaction, 1 unkown). This rate is very low compared to published data. In this cohort, demographical features had no association with persistence of therapy.

From logP to μFLUX. Physico-chemical profiling: past, present and future

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Pharmacokinetics of drugs is determined by their physico-chemical properties. For today physico-chemical profiling (PCP) became essential tool in drug design and a well-defined field of science. Since the pioneer work of C. Hasch, titled "The logP value and their use" javítandó: "The partition coefficents and their uses" (1971) the logP gained general usage as the measure of lipophilicity in medicinal chemistry and in QSAR. Beside lipophilicity the pKa and the steric parameters were also applied. There was a strong need for the development of new experimental methods including their standardization, validation and also to increase their capacity with miniaturization and robotics. Automated instruments for pKa and logP measurements were marketed. The exclusive role of logP changed in '90-ies due to the appearance of very low solubility APIs. The attention has been focused more and more to the solubility issue. The standardization of the methods which can provide precise reproducible solubility data meant and still means a challenge in PCP. The HT plate methods having high capacity, low material need but producing less precise results are suitable in early discovery phase while GLP conform methods should

be used later in the development phase. The measurements of extremely low solubility (<ng/ml), surfactants, polymorphs, co-crystals and micronized or nanonized compounds are in the front of the present PCP research. The last big change in PCP was the introduction of permeability as first kinetic parameter. The goal of all in vitro permeability methods (cell-cultured based, Franz-cell or PAMPA) is to achieve better IVIV correlation. The measurement in biomimetic media became general and dynamic methods being able to mimic better the living organism have also been developed. The high quality PCP data makes possible to improve the precision of prediction methods, particularly in case of solubility this will be the task of the near future. New perspectives were opened by the invention of μFLUX technique enables the study of dissolution and permeability together. The interest has turned to reveal the effect of additives on solubility and flux of APIs and thus to help the selection of the right excipients for the formulation. With this PCP has entered to the generic development. In the talk we present some results of our lab which significantly contributed to the above process.

The role of the pharmacy family Török in establishing the Hungarian pharmaceutical wholesale and industrial drug manufacturing

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Background: Due to historic reasons Hungary was unfortunately underdeveloped in most fields of the economy as compared to Western European countries. This also applies to the pharmaceutical wholesale and industrial drug manufacturing.
Aims: The lecture wishes to give an insight into the foundation of the first Hungarian pharmaceutical wholesale and industrial drug manufacturing by the Hungarian pharmacist József Török with an outlook on his beautiful pharmacy built in the 19th century.
Methods: The lecture is based on contemporary documents and periodicals to be found in the Museum of the History of Medicine and the National Archives in Budapest.
Results: The Hungarian family Török with a long-established pharmacy tradition is one of the founders of the Hungarian pharmaceutical wholesale and industrial drug manufacturing. József Török (1824-1899) pharmacist bought the pharmacy of Károly Gömöry (1779-1845) Hungarian pharmacist in 1854. Károly Gömöry (1779-1845) had a new pharmacy built in Pest (Király street) which was completed in 1813. Since Gömöry was fond of arts he entrusted Mihály Pollack (1773-1855) to plan the building of the new pharmacy. The decoration of the officina was prepared by Lőrinc Dunajszky (1784-1833) sculptor. The pharmacy run by József Török turned out to be a successful enterprise. Later he founded a pharmaceutical wholesale. He recognised the significance of advertisement. He advertised the medicine sold by his pharmaceutical wholesale to pharmacists in the Pharmacists' Yearbook and in other pharmaceutical periodicals, to doctors in medical brochures and to the public in local newspapers. He ensured free samples of the medicine to the doctors. Besides his two enterprises – the pharmacy and the wholesale company he expanded his business with the chemical factory "Galenus" which was founded by his son Sándor Török – also a pharmacist – and the Seits family. The first Hungarian pharmaceutical wholesale at 12 Király street operated from 1864 till its nationalisation in 1950 under the name of its founder József Török. After the nationalisation of the wholesale in the communist era it was merged into two other pharmaceutical wholesales under the name "Gyógyért" also located in Király street. "Gyógyért" was transformed after the democratic changes to "Hungaropharma" which has operated since then at 12 Király street.
Conclusion: The wholesale founded by József Török provided continuous supply of medicine to the Hungarian pharmacies until its nationalisation in 1950.

Dietary supplements: important part of the nutrition therapy

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Due to the unhealthy eating a lot of people need supplementation of micronutrients as well as healthy macronutrients. The latter ones are usually supplied with enteral or parenteral feeding however the micronutrients, inclusive vitamins, electrolytes and trace elements are taken as additional diet. Today, additional (concentrated) nutrients normally present in the food usually are not registered as pharmaceuticals but as dietary (food) supplements. The need of various dietary supplements is in general individual since people eat differently and the nutrient intake is different as well. Here I give details about some of the individual nutrients consumed in form of pharmaceutically formulated dosage forms like tablets, capsules solutions etc. in order to improve health condition. Today it is a fashion to take food supplements because of pre-

conceptions initiated by the advertisements however under certain conditions their use is justifiable and constitute nutrition therapy. I demonstrate evidences with regard to representatives of various nutrient groups, like fitonutrients, probiotics, the vitamin D and zinc.

How can herbal products fit into evidence-based medicine?

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Background: The use of herbal preparations for medicinal purposes is thought to be older than mankind, but it might be challenging for a traditionally used plant to become herbal medicine in accordance to today's regulations. Since the goal of our health care system is to provide the best possible care based on evidence-based medicine, it has become substantial that traditional medicinal plants tended to use as herbal medicines comply with those criteria that are set by either evidence-based medicine or legislation.
Aims: The aims of our work were to reveal the possible bases of the use of herbal medicinal products, and to facilitate the integration of plants and natural products into evidence-based medicine.
Methods: We have assessed European Union herbal monographs and scientific literature to identify those factors that might influence the classification of herbal medicinal products. Moreover, to dispel the misconception that the efficacy of herbal products cannot be proven scientifically, we have established the Hungarian Phytotherapy Study Group. Our Study Group performs the assessment of clinical trials on herbal medicinal products by preparing meta-analyses and systematic reviews to provide the highest evidence on the use of medicinal plants.
Results: Apart from promising in vitro and in vivo animal studies, numerous human clinical trials have been carried out to evaluate the efficacy and safety of plants and natural products. However, by analysing these clinical trials it has become clear that in many cases further and larger trials, performed by independent research groups and employing standard endpoints are needed to properly assess the efficacy and safety of herbal products.
Conclusion: It can be concluded that beside tradition there is a growing body of evidence supporting the use of herbal preparations. Monographs on herbal medicines are mostly based on tradition, but especially in cases of herbs used in Ayurveda, the European tradition is insufficiently documented; thus, it might happen that a plant with proven efficacy cannot be used as medicine. On the other hand, clinical trials of high quality are needed to establish monographs based on well–established use, and by assessing clinical trials, it has become clear that experts on plants are scarcely involved in clinical trials evaluating plants, and therefore the results of these trials are limited. To sum up, herbal products can be implemented into evidence-based medicine, but this process requires multidisciplinary cooperation.

Risk of falls and fractures associated with vitamin D therapies in scope of clinical trials

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Background: Scientific and clinical evidences documented that vitamin D is essential to maintain calcium absorption and consequently the normal funtion of the musculoskeletal system in human. The deficiency is rather endemic due to significant Vitamin D deficiency detected among most of population. Clinical trial data over the past decades clearly support the skeletal benefits of vitamin D supplementation in patients with circulating 25OHD levels of less than 30nmol/L. The role of vitamin D supplementation has been establashed for the indication also in prevention to minimize the risk of falls and fractures in general. However, the use of bolus or high-dose vitamin D supplementation in clinical trials among elderly people shown unexpeced adverse drug reactions and the need for further surveillance in dosing specifications of vitamin D therapies.
Aims: An overall goal is to establish the safety specificiaction of vitamin D supplementation for prevention and also in various medical conditions in order to minimise the risk of falls and fractures in elderly population. Additionally, to identify the risks associated with the most relevant life-style factors and nutritional conditions that may interfere with the success of vitamin D supplementation applied for prevenetion in general.
Methods: The results of clinical trials based on observational studies at clinical facilities and supported by survey in general public focused on alimentary, solar exposition, the use of dietary- and food supplementation but also assessed the edherence to given medications and other life-style factors.
Results: Vitamin D supplementation is indicated below 75 nmol/L, which is almost 90% of population among elderly and approx. 65-70% in general for the mass of population. The risk of fractures is signifi-

cantly higher among patients with low 25OHD levels (OR 2.83; CI: 1.51-5.31, p=0.007). But over 25% of population is not adherent to prescribed OP therapies. Alimenentary and life-style conditions are both needed optimal skeletal health: two-thirds of the subjects are underestimated their daily calcium intake, although only less then 30% of them are aware of the importance of calcium intake. Moreover, the physical activity level is being adequate in case of 28% even among the younger population.
Conclusion: The option of loading plus maintenance dose schedule proven to be efficient in cases of significant Vitamin D deficiency, however with proper nutritional and life-style conditions only in reduction of risk of falls and fractures.

Real-world data to facilitate assessment of health technologies: survival analysis of the treatment for non-small cell lung cancer

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Background: The use of real-world data is becoming increasingly important in order to generate real-world evidence for the assessment of health technologies in terms of clinical effectiveness and cost-effectiveness. However, the wide range of clinical data collected and stored in electronic medical records (EMRs) has not been used sufficiently for such purposes.
Aims: The aim of our analysis is to explore the facilitators and challenges of using EMRs to analyse the effectiveness of chemotherapy in non-small cell lung cancer patients.
Methods: EMR data from patients with advanced NSCLC who were treated at the University of Pécs between 2010 and 2018 were collected. Patients were grouped into two retrospective cohorts based on their first-line treatment: bevacizumab combination and pemetrexed combination. Follow-up was 3 years. A data mart was built with the use of Medsol Analyzer software. Dates of therapy induction and death were collected from structured fields, while data regarding disease progression (RECIST) were collected from unstructured tumour board documents. Kaplan Meier method was used for survival analysis.
Results: A total of 117 and 147 patients were included in the bevacizumab and the pemetrexed group, respectively. Baseline patient characteristics were similar in the two groups. The median overall survival was 525 and 388 (p= 0.0016) days respectively. The main challenge in data preparation was that important information on prognostic factors (e.g. smoking) or complications was not documented in a structured manner and that the date of progression can only be estimated indirectly using tumour board documents. The strength of the data was shown by the large number of parameters (e.g. TNM, ECOG, stadium, metastases, comorbidities) were available or could be generated about baseline characteristics of patients, making it possible to adequately compare the groups and that large volume of information generated at tumour boards enables to follow the therapies and the condition of patients using text mining methods.
Conclusion: EMRs are valuable source of data in the field of oncology, because the patient pathway is well describable due to the nature of the disease and the tumour board documentation provide very detailed and relevant data for analysis. However, data entry has to be improved to provide more structured information on prognostic factors and the progression of the disease. It is proposed to develop a standardized data model for storing the data generated in each Hungarian cancer centres, which could facilitate the use of real data for retrospective studies and for clinical trials (e.g. for external comparators).

Development of oral peptide drug delivery systems

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Background: The therapeutically used peptides are essential in the treatment of many diseases. At present these products are applied only parenterally and there is a great challenge to develop an oral pharmaceutical formulation and delivery system from these peptides. It is also one of the biggest challenge to set up an orally applied insulin drug delivery system. In my presentation, I would like to give an overview of the oral peptide delivery systems.
Aims: In our experiments, melatonin-concetrating hormone (MCH) has been used as a model compound. This hormone significantly affects the food intake and can be useful in the treatment of anorexia.
Methods: MCH was detected with a specific RIA system. Buchi B-395 Enapsulator apparatus was used to formulate alginate microcapsule as carrier system for MCH. First, special calibrations were required in order to ensure reproducible bead shape and size of the microcapsules (these parameters are: nozzle, electrode, vibrating system, frequency gener-

ator). Afterwards the active substance (MCH) was incorporated in microcapsules. The cytotoxicity of components and various penetration enhancing excipients used in the formulation of the delivery system was examined on human adenocarcinoma Caco-2 cell line. In vitro dissolution test was performed for the release of MCH from the beads, followed by a specific RIA examination in order to detect MCH concentration. In addition, the beads swelling properties and the particle size distribution was examined with laser diffraction analysis.
Results: We determined the most important physical properties of the microparticles. The API enclosure and dissolution were also evaluated in vitro. In addition, our in vitro investigations showed on CaCo-2 cell monolayer that all of the excipients of the formulation is safe in the applied concentration. Moreover, we demonstrated that the applied penetration enhancers influence the junctional function (ZO1, Clau1, BCat) of the monolayer. According to the performed Caco-2 transmembrane investigation the abovementioned penetration enhancement had been demonstrated after determination of in vivo MCH absorption from rat blood samples by specific RIA.
Conclusion: Our results indicated that the alginate-penetration enhancing materials containing microcapsules provide a useful opportunity for the development of an oral peptide drug delivery system

The use of complementary therapy in biological therapy patients with rheumatologic and dermatological diseases in a university clinical center

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Background: Biological therapies have revolutionized the treatment of dermatological, rheumatologic and gastroenterological chronic conditions. These chronic inflammatory diseases are usually linked with high rate of complementary and alternative therapy use and we do not know whether these products affect the effectiveness and safety of therapies.
Aims: As there are limited studies regarding biological therapies and complementary therapy use in Hungary, our aim was to assess the frequency and reason for supplement use in patients getting biological therapy.
Methods: 26 dermatological and 37 rheumatologic patients were interviewed through structured personal interviews at the point of dispensing. The personal medication use review was completed with the review of medical records. The questionnaire focused on drug and supplementary product use (dietary supplements, herbal remedies, etc.).
Results: 32 women and 31 men completed our survey and they have been receiving biological therapy for an average of 6.5 years and in case of 33% there was a switch in the therapy. Beside the prescribed medicines (6.6/patient) patients were taking averagely 2.3 (1-8) supplementary products as well and 52.4% used at least 1 dietary supplement or herbal medicine. The main motivations for complementary therapy use included prevention or treatment of side effects (e.g.: liver damage) and to reduce anxiety (magnesium and vitamin B_6). Potential drug-supplement interactions included: Omega-3 fatty acids and clopidogrel, calcium/magnesium salts and glucocorticoids, *Matricaria recutita* and *Ginkgo biloba*.
Conclusion: The increasing effectiveness of biological therapies can be seen in the study population, however there is a limited data regarding factors affecting these therapies, especially when it is the last therapeutic option. Therefore, and because of their costs, it is essential to identify drug-supplement interaction that may compromise biological therapy patient care. With the involvement of hospital and clinical pharmacists in the dispensing of biological therapeutic medications, there is a greater chance of for the optimization of these therapies.

Modulation of nose-to-brain delivery of a P-gp (MDR1) substrate model drug in anesthetized rats

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Background: During the last decades several new drug formulations were developed to target the CNS from the nasal cavity. The advantages of the intranasal drug administration are the 1) bypass of blood-brain barrier, 2) lower doses needed 3) less systemic side effects, 4) no first pass metabolism 5) rapid absorption and pharmacological effects. However, in these studies less attention was paid to the possible drug-drug interactions in case of multi-drug therapy.
Aims: The aim of the current study was to identify the possible functional role of P-glycoprotein in the drug absorption in nasal cavity and detection of drug-drug interaction by measuring brain and blood concentrations of our test drug.
Methods: In a pilot study quinidine was administered as a nasal solution, and then we moved on with gel formulation. A P-gp substrate model drug, quinidine was tested by IN administration in presence of PSC-833 (specific P-gp inhibitor) given IV or

IN and adrenaline (IN) at low (50ng) or high (20g) dose. The brain and blood levels were monitored using dual-probe microdialysis.
Results: In control animals the brain penetration of quinidine was at the level of detection limit, but in combination therapy with IV PSC-833 the brain levels increased dramatically, similarly to high dose IN adrenalin, where due to vasoconstriction peripheral distribution was blocked.
Conclusion: These results indicate that P-gp has a crucial role in drug absorption and efflux at nasal cavity, while adrenaline is also able to modify the penetration profile of the P-gp substrate model drug at nasal application.

Medication use review (MUR) in community pharmacies – an international pilot program – preliminary report

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Background: Medicines Use Review (MUR) is a structured evaluation of patients´ medication use aiming to decrease drug related problems and increase efficiency of drug treatment. MUR service could be provided by different healthcare specialists – GP, nurse and pharmacist, but in many countries MUR service is mostly offered by pharmacists.
Aims: A pilot project is designed to evaluate professional competency of community pharmacists about MUR and impact of MUR service to patient's knowledge about medication use.
Methods: Patient inclusion criteria: patients with polypharmacotherapy (5 and more medicines), adult, but no other age limits. GPs advise patients to turn to community pharmacy where MUR service is available. During the first visit, the patient is registered to the service, personal details and general perception about medications will be documented at pharmacy. During the second visit, the MUR service will be provided with feedback to GP and patient and the third visit will be assigned after about one month. During the third visit, the repeat MUR service will be provided if necessary, but the main focus is oriented to patient´s feedback to their condition and possible problems with still existing with use of medication.
Results: 5 pharmacies participate in the pilot project working with 17 GPs. 66 patients have started MUR service until now, their age on average 68 years, two third of participants are female (49:17). Our study group takes an average of nine daily medications, the highest number was 20. The patients were satisfied with MUR service. GPs' gave controversial feedback, some of them find it useful but others were sceptic about achiving goals. Challanges indicated by pharamacists regarding the service: time constriants and extra efforts required for documentation.
Conclusion: In the future it would be important to increase pharmacist-led MUR service at the community pharmacies because it can contribute to improving the safety of outpatient therapy.

Solubility analysis and real time dissolution monitoring of polymorphs

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Background: Polymorphism of drug substances plays an important role in drug research and development. Due to the different crystal structures, the polymorphs may differ in their physico-chemical properties such as stability, solubility or dissolution rate, and therefore can significantly influence the bioavailability of the substance.
Aims: The aqueous solubility and dissolution profile of different polymorphic forms of venlafaxine hydrochloride, oxytetracycline hydrochloride and carvedilol were investigated.
Methods: The pH-dependent aqueous solubility over a wide pH range was measured by validated saturation shake-flask method at 25°C. The solid form present at the solubility equilibrium was identified by X-ray powder diffraction and Raman spectroscopy. The dissolution kinetics was also studied using real time concentration monitoring applying fiber optic UV probes.
Results: In the case of venlafaxine hydrochloride, no difference was found in the equilibrium solubility of the two polymorphic forms in the pH range 7.5-12. In aqueous buffer solutions the polymorphs transformed to a common product. In the case of oxytetracycline hydrochloride, no significant difference of equilibrium solubility values was found in the pH region 4-7.4 between the two polymorphs. The solid phase analysis proved that both forms were converted to an identical dehydrate form. However, in simulated gastric fluid (SGF) at pH 1.2 the metastable Form B showed 1.9 times higher solubility than Form A. The dissolution performance showed also significant difference between them in SGF. In the case of carvedilol, twofold difference was found between the equilibrium solubility of the two polymorphs in the pH range 7-10. It was proved that the crystal structure of the two polymorphs did not change during the measurement. Moreover, the real

time monitoring of dissolution revealed their significantly different kinetics, the faster dissolution and the higher supersaturation concentration of kinetic Form II. In the acidic pH range Form I and Form II precipitated as common salt.
Conclusion: This study illustrates three different possible behaviours of polymorphic substances, and the great importance of the solid state characterization at the beginning and at the end of the solubility and dissolution experiments to provide accurate information on possible transformations.

Standardisation of of quality parameters of plant originated drugs during the production with special respect to the cultivar use

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Background: In case of plant originated drugs, the quality requirements of the Ph.Eur. are frequently not satisfied. In order to take appropriate mesures for standardisation, it is necessary to recognise the background which influences the final quality already during the plant life or postharvest proccessing.
Aims: The presentation summarizes the most important factors in determination of drug quality and the possibilities to optimise them with special focus on the role of the intraspecific varieties.
Methods: The results are discussed based on own experimental results on different medicinal plants beside a wide range of scientific references. Numerous examples will be presented.
Results: In numerous plant species different chemotypes can be observed both in natural populations and selected accessions. In Hungary, we have currently 58 registered cultivars which, however belong to 29 species. It means, that for many species there is hardly any choice of varieties. Additionally, several cultivars have primarily been developed for higher yield, resistance or other technological features and active compound content was only a secondary goal. Nevertheless, outranging Hungarian cultivars are known for poppy, marjoram, fennel, fewerfew, among others. The manifestation of the inherited genetic potential, however depends on the ontogenetic phase and on the examined plant organ. Changing environmental conditions contribute directly or indirectly to the instability of the drug quality, too. Genotype-environment interaction seems to be not neglectable either, but unfortunately, this is until now a less investigated subject.
Conclusion: High output cultivars represent the primarily basis for stable plant drugs. However, in many cases the required quality parameter is a complex or a marker compound (e.g. total flavonoid content) which is presents an aggravating factor in breeding. For manifestation of genetic background an assuring a pharmacopoea conform quality, establishment of cultivar specific technologies are also necessary.

Investigation of antimetastatic properties of potential anticancer compounds in vitro

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Background: Currently cancer is the second major cause of mortality globally but a transition in the predominant causes of deaths is detected in high-income countries: mortality from cancer became more common than that from cardiovascular disorders.
Aims: Concerning cancer-related mortality, up to 90% of solid tumors is due to consequences of metastasis indicating that antimetastatic pharmacological interventions may have a crucial impact on the overall mortality.
Methods: Metastasis formation is a complex and well-organized procedure including the infiltrating cancer growth through the extracellular matrix, migration and initiation of distant colonies. Identification of innovative antimetastatic compounds requires in vitro methods of relatively high throughput.
Results: The aim of the presentation is to give a summary of the currently available antimetastatic methods including matrix metalloproteinase assay, different types of cell-based migration and invasion assays.
Conclusion: Some preliminary results obtained at our Department will be additionally presented.

SHORT PRESENTATION

Biocompatibility and dissolution measurements of different 3D printed drug delivery systems

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Background: 3D printing is a modern technique which can be used in numerous fields like in the pharmaceutical industry. This technique enables to manufacture complex, personalized products on-demand.
Aims: Our aim is to manufacture different drug delivery systems which can be used for personalized medication or manufacturing of orphan drugs.
Methods: For the 3D printing we use Fused Deposition Modelling (FDM) technology with PLA, PMMA and PET polymers. The printed samples material structure is characterized by SEM, FTIR, PALS and contact angle measurements. Biocompatibility is a compulsory examination through the development so with our colleagues we developed a long-term modified MTT assay which is a high efficacy screening test. For the final interpretation we also performed biofilm formation with crystal violet assay to gain extensive information. The samples dissolution profile is examined with an Erweka USP type I apparatus with automatic sampling system at pH=7.4 for 24 hours.
Results: Based on the biocompatibility results we determined the samples non-cytotoxic but with the results of biofilm formation we can sort out the most proper polymer for further examinations. The material structure was determined and the FTIR spectra proves the side-chain modification of the polymers. The samples dissolution profile can be affected by the variation of the diameter and the infill percentage through the 3D printing technique.
Conclusion: Based on the determined data we have successfully printed 3D samples in runs up to 50 units which are non-cytotoxic and has good material structure properties. Based on the results the applicability of the different samples can be determined and it can give us information for the scale enlargement.

Acknowledgement: The project was supported by the Gedeon Richter's Talentum Foundation (1103 Budapest, Gyömrői út 19-21 Hungary). The research was financed by the Higher Education Institutional Excellence Programme (NKFIH-1150-6/2019) of the Ministry of Innovation and Technology in Hungary, within the framework of the Therapeutic purposes thematic programme of the University of Debrecen. The project was supported by the EFOP-3.6.1-16-2016-00022. The project is co-financed by the European Union and the European Social Fund.

References: 1 Arany, P. et al.; Pharmaceutics 2019;11:277; 2 Boetker, J. et al.; Eur. J. Pharm. Sci. 2016;90:47-52.

Synthesis of twin-nucleosides

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Background: Natural nucleoside derivatives play pivotal role in many biological processes, while synthetic nucleoside analogues are used in several areas of medicine, e.g. in the anticancer or antiviral chemotherapy [1]. Therefore, the design and synthesis of nucleoside analogues is an important topic of chemistry. Morpholinos, containing a morpholine ring instead of the furanose, represent a valuable class of nucleoside analogues [2]. These compounds are obtained by the reaction of the corresponding 2',3'-dialdehyde derivative of nucleosides with ammonia or alkylamine (R-NH2) under reductive conditions.
Aims: We planned to synthesize new nucleoside dimers, consisting of a nucleoside and a morpholino, creating a direct linkage between the morpholine nitrogen and the 5'-carbon of the nucleoside, to produce so called „twin-nucleosides".
Methods: Two types of monomeric units were prepared for the synthesis of dimers. On the one hand, the appropriately protected nucleosides were oxidized into 2',3'-dialdehydes with NaIO4. On the other hand, 5'-deoxy-5'-aminonucleosides were synthesized. The amines and aldehydes were coupled in various combinations in EtOH, using NaCNBH3 as reducing agent.
Results: Purine and pyrimidine nucleosides: uridine, ribothymidine, thymidine, adenosine, and inosine were involved into the reactions. Seven new dimers were obtained (including homo- and heterodimers), and also a trimer and a tetramer were synthesized, by elongation of the shorter oligomers at position 5' of the morpholino unit.

Conclusion: A new type of oligomeric nucleoside analogues were synthesized, creating a tight bond between the monomers. We are planning the synthesis of further dimers using other nucleosides or other combinations of the monomers, incorporation of a twin-nucleoside into normal oligonucleotide for hybridization studies, as well as the biological evaluation of the obtained dimers in cytotoxicity and antiviral assays.

Acknowledgement: Supported by the ÚNKP-19-3 New National Excellence Program of the Ministry for Innovation and Technology. The research was also supported by the EU and co-financed by the European Regional Development Fund under the projects GINOP-2.3.2-15-2016-00008, GINOP-2.3.3- 15-2016-00021 and GINOP-2.3.3-15-2016-00004.

References: 1 Jordheim, L., P., et al. Nat. Rev. Drug Discov. 2013;12:447-464; 2 Khym, J., X., Biochemistry, 1963;2:344-350.

Investigation of the permeability and cytotoxicity in novel topical ophthalmic formulations using in vitro and ex vivo models

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Background: Research and development are big challenge in the field of ocular drug delivery. Suitable drug penetration is a key factor, meanwhile negative effects of reflex mechanisms and complex anatomical structure limit the therapy. Besides the therapeutic efficacy, the antimicrobial stability must be ensured during the application and storage. Novel preservative alternatives are required, considering the toxic attributes of widely applied benzalkoniumchloride (BK). Prednisolone (PR) containing eye drops were developed by our research group, where cyclodextrin (CD) derivatives and antimicrobial biopolymer were applied. The results of increased in vitro drug diffusion, acceptable viscosity, mucoadhesion and antimicrobial effectiveness test were previously published [1].

Aims: Our aim was to confirm the compliance of developed eye drop formulations by investigation on cytotoxicity and permeability models. By application of preservative biopolymer and CD additives, a biocompatible, non-toxic composition is created which can be an innovative approach in the therapy of inflammatory eye diseases.

Methods: In vitro permeability and toxicity were investigated on transformed human cornea epithelial cell line (HCE-T). The cytotoxicity was tested by impedance measurement and immunohistochemistry methods. Ex vivo permeability was tested on porcine cornea model. The quantitative analysis of samples from permeability studies was performed by HPLC.

Results: The results of impedance measurement show that BK containing formulations have significant cytotoxic effect on the HCE-T cell culture model, meanwhile in the case of antimicrobial polymer containing compositions have no cell damage. That was confirmed by the immunohistochemistry assay. As the in vitro permeability test on HCE-T shows, significantly higher permeability of PR was seen in the case of CD and biopolymer additives containing solutions in comparison with the PR suspension. In the case of ex vivo permeability test, no significant change was obtained by applying the CD, although slower drug release is expected from delivery systems with biopolymer.

Conclusion: Considering the results of in vitro and ex vivo assays, the developed ophthalmic formulations could be innovative approaches, where favourable drug permeability and non-toxic attributes are expected. Taking into account the mucoadhesion and solution form, suitable therapeutic effect, less irritation and better patient-compliance can be achieved.

References: 1 Bíró et al., Drug Des Dev Ther 2018;12:2529–2537.

Rheological investigation of human sputum in cystic fibrosis

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Background: Cystic fibrosis (CF) is one of the most common progressive genetic life-limiting disease, in which the defect in cystic fibrosis transmembrane conductance regulator proteins (CFTR) leads to an imbalance ion-water equilibrium resulting in dehydration of the sputum; increased concentration of mucus and thus increased viscosity. The high viscosity mucus contributes to the low clearance of the surface liquid, which leads recurrent infections and a chronic inflammation and subsequent progressive lung damage.

Aims: The aim of our study was to work out an adequate protocol to measure the rheological properties of human sputum (HS) and analyse the effect of the locally administrated mucolytic agents in vitro.

Methods: Rheological oscillatory tests were applied to investigate the mechanical properties of the human sputum samples: time sweep tests in order to determine a holding time before the measurement; and then frequency sweep tests were performed the present the real structure of the mucus gels.

Results: The time sweep investigation indicated a structure build-up during the measurement which can be explained by the destruction effect of the sample insertion into the instrument and/or the thermogelling of the samples at body temperature in the instrument. Addition of mucolytic agent before the measurement this structure build-up was elongated, or absolutely missing, but in some cases any differences could not be observed compared with the non-treated sputum. On the basis of the average G' value of the non-treated samples during the frequency sweep tests the human sputum samples can be categorized into 3 categories: high elastic samples; viscoelastic gels and viscoelastic liquids. The effect of the mucolytic agents (ΔG') were calculated from the G' values of the treated and the not-treated samples, and it was established there is no statistical differences among the additive types.

Conclusion: The constant handling of the sputum sample before the measurements is very important. The in vitro treatments indicated the liquefactions of the samples due to the treatment, but statistical differences could not be stated among the different additives, which suggest the dilution effect of the solution dominated.

The work was supported by EFOP-3.6.2-16-2017-00006 „LIVE LONGER – Modern orvostudományi diagnosztikus eljárások és terápiák fejlesztése transzlációs megközelítésben: a laboratóriumtól a betegágyig"

Historical evaluation of Transylvanian Ethnobotanical data in herbal books and manuscripts

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Background: Regions of Transylvania inhabited by Székely and Csángó people have been studied for ethnobotanical and ethnomedicinal data. Our team surveyed settlements in the Homorod Valley, Úz Valley, and Covasna County focusing mostly on plants' use in human and veterinary ethnomedicine (2007-2019). Based on these collections, plants were listed and compared to data obtained from databases to select species for historical and medicinal study.

Aims: According to our collections, the goal was to sum historical and (ethno) medicinal data of four selected species namely *Anthyllis vulneraria* L., *Lathyrus tuberosus* L., *Lysimachia nummularia* L., and *Tanacetum balsamita* L. in earlier Transylvanian and other Central European herbal books.

Methods: Ethnomedicinal records of the selected four species were collected from works between 16-19th century (Olosz 2002). In Transylvania, printed (Melius: *Herbarium*, 1578; Beythe: *Fiveskönyv*, 1595; Pápai Páriz: *Pax corporis*, 1690; Juhász: *Házi különös orvosságok*, 1761), and handwritten works (Lencsés: *Ars medica*, 1577 k./Varjas, 1943; *Orvosságos könyv*, 1677; Gellen G. 1680; Gellen I. 1714) were studied for the historical background of Hungarian prescriptions of plant origin. These records were compared to those of Béla Radvánszky's collection on books published about old Hungarian human and veterinary medicine (Hoffmann ed. 1989).

Results: Some earlier examples for the selected species: data of *A. vulneraria* and wounds occur from 1807 for kidney disorders and diabetes, and in plant list in Pápai's 1690) and Benkő's work (1770-1790). Lathyrus genus is described from 1471. *L. nummularia* was mentioned as *fillérfű* (1824) by Béla Práter for sprain. *T. balsamita* was documented in the 17th century (Hoffmann ed. 1989), and as *lapos menta* (Lexicon Budense 1825) and *gilisztahajtó* for endoparastites as a tea in Székely Land.

Conclusions: Historical relationship of ethnomedicine and medical science can support the interpretation of their different and similar aspects. Historical evaluation confirms the significant influence of official medicine to ethnomedicine in many centuries. Based on the interaction of Transylvanian (Hungarian, Romanian, and Saxon) traditional elements, several analogue treatments can be mentioned these days.

Acknowledgement: This work was supported by a grant from the OTKA (Hungarian Scientific Research Fund, K 127944).

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The mode of action of thyme (*Thymus vulgaris* L.) essential oil in an endotoxin-induced acute airway inflammation in vivo model

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Background: Respiratory tract diseases (RTDs) affect a large number of people worldwide. One of the traditional application modes of essential oils is the

inhalation. RTDs generally are associated with infection and inflammation at the same time. However, the anti-inflammatory effect of essential oils is poorly studied in vivo. Transient Receptor Potential Vanilloid1 (TRPV1) and Ankyrin1 (TRPA1) ion channels are expressed on the sensory neurons and epithelial cells of the airways and play a role in sensory-immune interactions.

Aims: Therefore, we aimed to examine the chemical composition and effects of thyme oil (TO) inhalation in the endotoxin (LPS)-induced acute airway inflammation mouse model and the potential role of TRPA1/V1 ion channels in mediating TO effect. The essential oil was selected on the basis of its potent antibacterial activity.

Methods: The chemical composition of TO was determined by GC-MS. Lung inflammation was evoked by the intratracheal administration of 60μL LPS (*E. coli* 083) in female *TRPA1/V1*+/+ (WT) and *TRPA1/V1*-/- (KO) mice. TO or the control oil was inhaled 3 times for 30 min during the 24-h period of the experiments. Airway function was measured in awake, spontaneously breathing animals by unrestrained whole-body plethysmography. Lung myeloperoxidase (MPO) activity was determined by spectrophotometry. The histopathological alterations were evaluated from hematoxylin-eosin stained lung sections by semiquantitative scoring.

Results: Thymol (46.3%) and p-cymene (22.1%) were the two main components of TO. TO inhalation significantly decreased airway hyperreactivity in WT, but aggravated it in KO mice. Histological parameters were not affected significantly by TO inhalation in either WT or KO mice. LPS treatment induced a remarkably increased MPO activity, which was significantly reduced by TO inhalation in WT, but not in KO mice.

Conclusion: Therefore, thyme oil can be considered as a potential treatment in airway inflammation, and its protective effect is potentially mediated by TRPA1/V1 ion channels.

Stability study of nasal powder formulation containing nanosized lamotrigine

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Background: The nose offers a great possibility to avoid adverse events and increase the patient compliance. Due to its advantageous properties local, systemic and central nervous (CNS) system effects are also available. The application of innovative and efficient products, that are containing nanoparticles, may lead to the improvement of different therapies. The quality insurance of the pharmaceutical products has received considerable attention in the past few years. That is why the stability of the formulations has become extremely important and therefore, quality influencing parameters need to be kept near constant during the transport, storage and application. Generally, solid dosage forms (e.g. nasal powders) have better stability than liquid formulations.

Aims: The aim of our study was to carry out the long-term stability study of a previously developed nasal powder (NP) formulation, which contained nanosized lamotrigine (LAM).

Methods: Stability tests were performed in Binder KBF 240 (Binder GmbH, Tuttlingen, Germany) equipment, with a constant-climate chamber. The long-term stability test was performed according to the ICH Q1A guideline, at 25 ± 2 °C with 60 ± 5% relative humidity. To justify the unchanged parameters, different properties were investigated. The particle size and morphology were examined by SEM (Hitachi S4700, Hitachi Scientific Ltd., Tokyo, Japan). Structural investigations (XRPD, DSC) were also carried out. The in vitro dissolution profiles were determined spectrophotometrically at 307 nm with an ATI UNICAM UV–VIS system. A self-developed, horizontal diffusion apparatus was used for in vitro permeability testing.

Results: The particle size of LAM in the NP (97 ± 60nm vs. 239 ± 116nm) formulation was near constant. The results were confirmed by SEM pictures, which did not show particle aggregation. The structural investigations showed that the LAM remained partially amorphous. The in vitro dissolution rate was around 80% after 5 mins both at the beginning and at the end of the study.

Conclusion: During the test period no considerable change occurred in the powder formulation, as the examined parameters were nearly unchanged according to the results of the investigations. This is beneficial, because it means that the patients could receive their medication in proper quality.

References: 1 Gieszinger P et al. Drug Dev Ind Pharm, 2018;44(10):1622-1630

Formulation and characterization of a verapamil containing low-density gastroretentive dosage form

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Background: Gastroretentive drug delivery is useful

when the active ingredient has narrow absorption window or gastric targeted release is aimed. One of the retentive mechanisms is the floating by low density. If the density is below 1g/cm^3, the formulation floats on the gastric-fluid, and avoids the elimination from the stomach.

Aims: We aimed to develop a verapamil containing drug delivery system based on its high-porosity and low-density by foam formation after melting the components [1].

Methods: We used the following materials for our work: PEG 4000, stearic acid and verapamil for formulation. We prepared different compositions by continuous production and determined the basic parameters such as weight and density. We made micro-CT images to get information about the pore size and distribution. We also tested the in vitro drug release in 1.2 pH buffer and texture changes during dissolution. Finally, we made animal experiments to prove the modified release and gastro-retention of the formulation.

Results: We reached less, than 0.9g/cm3 density in all of the formulations. The micro-CT images showed homogeneous distribution of the cavities in the matrix and closed cell structure. The pore size was between 200 and 300μm. The prepared foams had hard structure even at body temperature that was measured by texture analyzer. The dissolution studies showed prolonged drug release up to 10 hours, when 80% of the API was dissolved. At the end of the dissolution test the water uptake reached 75% of the total mass and the weight of the formulation decreased to 25% of the initial mass. Following the process, we detected dry, hard core until 5 hours of dissolution. After that, we aimed to prove the gastro retention ability of formulations in rats, so we created small samples with 30% $BaSO_4$ as a contrast material. The sample stayed in the rat stomach for 2 hours until the total erosion, that was measured by texture analyzer also.

Conclusion: In summary, we prepared and characterized a solid and low-density drug delivery system with zero floating lag-time. The prepared samples showed prolonged verapamil release and hard structure with the ability to remain in the stomach for several hours.

References: 1 Vasvári et al. AAPS PharmSciTech, 2019;20:7

Alteration of the cell membrane – a novel method in the pain modulation

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Background: The Transient Receptor Potential ion channels, such as Vanilloid 1 and Ankyrin repeat domain 1 (TRPV1/A1) are expressed in nociceptive primary sensory neurons. These channels are widely studied, but there are some missing information about their modulation. Noxious heat, capsaicin (CAPS), resiniferatoxin (RTX), fatty acid metabolites activates TRPV1. TRPA1 can be activated by noxious cold, mechanical stimuli and formaldehyde. Lipid rafts are specific membrane domains, which are rich in cholesterol, sphingomyelin and gangliosides, and create functional complexes with TRP channels. Sphingomyelinase (SMase) is an enzyme, which hydrolyzes the membrane sphingomyelin content, while myriocin (Myr) an enzyme inhibitor, which blocks the de novo sphingolipid synthesis. Our group previously described, that the treatment with SMase or Myr inhibits the function of TRP receptors in vitro [1-2].

Aims: We examined the potential antinociceptive effect of SMase and Myr in different in vivo mouse models, and also tested some in vitro properties.

Methods: Capsaicin-evoked acute nocifensive ("eye-wiping") test, formaldehyde-evoked hyperalgesia, and RTX induced thermal allodynia and mechanical hyperalgesia model were performed to investigate the effect of SMase and Myr. The in vitro properties were tested by fluorescent spectroscopy.

Results: Both SMase and Myr decreased the CAPS-evoked "eye-wiping" movements, and Myr has a prolonged effect in this model. SMase largely reduced the formaldehyde-caused nociceptive behavior in the second phase, while Myr did not have any effect. In the RTX-model both compounds reduced the thermal allodynia, and SMase had significant effect also in the mechanical hyperalgesia. In the fluorescent spectroscopy SMase did not modify the Laudran spectras.

Conclusion: On the basis of our results, we assume that the hydrophobic interactions between the TRP channels and lipid rafts might be a promising drug target in the future.

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Implementation of digital pharmaceutical technology in the practical education of graduate pharmaceutical students at Semmelweis University

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Background: The essential characteristics of a pharmacy student among others is the openness and curiosity towards digital technology. In the age of information, when breakthrough technologies and approaches turn up within a few years, the education system and universities have a great responsibility in this respect. The lecturers at the cathedra face day by day a noble challenge: somehow they have to prepare students not just for the questions of "today" but also for the answers of "tomorrow". 3D printing is gaining more and more attention and have a great potential in the future of pharmaceutics. Deploying the benefits of this technology (e.g. flexible, patient-based medication) in a community/hospital pharmacy, could help to satisfy the diversified demands of patients through the added-value of pharmacists.
Aims: The aim of the study was to check the knowledge of 4th year pharmacy students at Semmelweis University about digital technology and 3D printing and to introduce them the theoretical and practical fundaments of 3D printing. The investigation of attitude, opinion and knowledge before and after the 135 min long practice was also put into the focus.
Methods: The theoretical knowledge and attitude of students regarding 3D printing were screened with a questionnaire on voluntary basis. The questionnaire involved 8 questions (single or multiple choice) and had to fill before and after practice. The information was collected anonymously, online via a QR code or paper-based. The designing, slicing and printing steps were demonstrated by an FDM printer. Conventional, round, polylactic acid-based tablets were printed.
Results: Willingness on filling out the questionnaire was 96.8%. Approx. 60% of participants had no experience with 3D printing and 25% of students estimated moderately useful to learn about 3D printing. After the practice 96% regarded it as very worthy. More than 50% believed that the formulation of patient based medicines at a hospital pharmacy is feasible within 5 years. One of three students considered the completion of GMP requirements as a great challenge.
Conclusion: The 4th year pharmacy students at Semmelweis University were satisfied with the implemented practice and judged it as useful. The mysterious nature of this technique has been dissolved and they see a great potential in 3D printing but some limiting barriers were also revealed.

Polymeric micelles as promising tools to substitute surfactants in the dissolution of poorly water soluble drug

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Background: In the recent years the application of surfactants to increase the wetting properties and therefore to overcome the hurdles of drug dissolution and absorption in oral drug delivery is decreasing because of their disadvantageous properties. Soluplus® (BASF GmbH, Germany) a novel solubilizing amphiphilic graft co-polymer, offers the possibility of a good solubility enhancement in combination with a fast dissolution through polymer micelle forming. Melt technology is an appropriate green technology, to produce solid dispersions involving these surfactants in an inert carrier or matrix in the solid state.
Aims: Our aim was to develop a solid drug delivery system (DDS) using melt technology to design such carrier systems which are based on crystalline eutectic and additives with various solubility enhancing agents.
Methods: In the present work two solubilizers (Cremophor® RH 40 and Soluplus®) were tested for its capability to improve drug dissolution. As model drug the lipophilic, poorly water solu-ble megestrol acetate (MEGA) was chosen. The basis of the carrier were two sucrose alcohols, xylitol (XYL) and mannitol (MAN), which form eutectic mixture in certain ratio with PEG 6000. The solubilizers were dispersed with the MEGA in the eutectic carrier by fusion meth-od. The phase diagram of eutectic compositions of the carrier was determined using DSC. In vitro dissolution studies were carried out on gastric pH to investigate the release kinetic of the compositions with different solubilizers in comparison with pure MEGA containing carrier.
Results: DSC measurements showed that the XYL and the MAN formed eutectic mixture with each other, as a result the melting process could be carried out on decreased temperature [1]. The dissolution studies of the developed formulations showed increased dissolution rate in case of solubilizing agent containing products, even after tenfold scale up process.
Conclusion: We developed a carrier from XYL-MAN eutectic and PEG 6000 ternary system. It was found that the Soluplus® had a high solubilization capacity, thanks to form polymeric micelles, which encapsulates partly the MEGA during dissolution. Increas-

ing quantity of graft copolymer resulted in higher amount of dissolved drug, therefore it is suitable to have DDS with controlled drug release. We can conclude an innovative "value added" solid formula of MEGA, which can be suggested for the patient for ex tempore sus-pension preparation before administration.

Acknowledgement: This work was supported by the National Research, Development and Innovation Office, Hungary (GINOP-2.3.2-15-2016-00060).

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Microstructural distinction of antiemetic drug-loaded nanofibrous orally dissolving web formulated with different excipients

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Background: The hydrophilic polymer-based electrospun fibrous orally dissolving webs are promising candidates for rapid drug release, which is due to the high surface area to volume ratio of the fibers and the active ingredient can be incorporated in the polymer matrix in amorphous state. However, the enhanced molecular mobility of these materials is responsible for their physical and/or chemical instability.
Aims: The aim of the project was to prepare poly(vinyl alcohol)-based, metoclopramide hydrochloride-loaded electrospun nanofibers using either polysorbate 80 (PS80) or hydroxypropyl-β-cyclodextrin (HP-β-CD) and tracked how the excipient influences the fiber formation process, the mechanical properties, macro- and microstructures of the electrospun samples and the drug release from the nanofibers.
Methods: The electrospun samples were subjected to several imaging techniques: Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM), and complex physicochemical characterization (with Positron Annihilation Lifetime Spectroscopy (PALS), X-ray Diffractometry (XRD) and solid-state Nuclear Magnetic Resonance (NMR) spectroscopy) the fibrous delivery systems was carried out which were enabled the better understanding the supramolecular interactions of multicomponent systems.
Results: SEM verified that clearly fibrous structures were obtained, without any beads and film-like areas. The mechano-manipulation of AFM revealed that the usage of PS80 led to about two times stiffer, less plastic fibers than the addition of HP-β-CD. The cross-polarization build-up curves of 1H-13C NMR spectroscopy verified that CD is an inner plasticizer, while PS80 acts as an outer plasticizer and can migrate in the polymer matrix, which is due to its "liquid-like" behavior. PALS measurements also showed the enhanced mobility of the PS80 containing formulation and the molecular packing enhancer properties of the HP-β-CD. XRD method suggested that as a result of the fiber formation process the active pharmaceutical ingredient incorporated into the fibers in a purely amorphous state, but the ssNMR pointed out that usage of the examined additives enabled the development of a molecularly dispersed system of different homogeneities.
Conclusion: In case of both formulations clearly fibrous structure and molecularly dispersed system were formed. It was also showed that PS80 and HP-β-CD render distinct mechanical properties of the fibers, as PS80 advances elastic behaviour and HP-β-CD promotes plastic features.

Determination of enantiomeric purity of esomeprazole by capillary electrophoresis

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Background: Esomeprazole, as a proton pump inhibitor, is one of the most effective agents used in gastric hiperacidity-related disorders. It is a pyridinyl-methyl-sulfnyl-benzimidazole derivative with an asymmetric sulfoxide group in its structure. It was the first proton pump inhibitor introduced as enantiomerically pure compound in the therapy.
Aims: The aim of this study was to develop and validate a suitable separation method for the determination of the enantiomeric purity of the compound of interest using cyclodextrin-mediated capillary zone electrophoresis.
Methods: Different native and derivatized cyclodexrins were screened as chiral additives, using phosphate buffer at pH 2.5 as background electrolyte, in order to find the most suitable chiral selector for the separation of omeprazole enantiomers. Apparent complexation constants of the enantiomer-cyclodextrin complexes were determined in order to investigate the possible mechanism of enantiomeric separation. The effect of analytical conditions as temperature, applied voltage and buffer concentration was also evaluated in order to find optimal separation conditions.

Results: Baseline chiral separation of the two enantiomers with favorable migration order (R-omeprazole migrates first) was achieved in less than ten minutes using the following conditions: a 50mM phosphate buffer at pH 2.5 as background electrolyte, 20mM randomly methylated β-CD as chiral selector, +20kV applied voltage and 20°C system temperature, and UV detection at 210nm. The method was validated according to current guidelines and proved to be reliable, linear, precise, and accurate for the determination of 0.2% distomer as chiral impurity in esomeprazole samples.

Conclusion: A rapid and cost-effective capillary electrophoresis method was developed for the separation of omeprazole enantiomers. The optimized and validated method proved to be suitable for the determination of enantiomeric purity of esomeprazole from pharmaceutical preparations and could represent an alternative for the available compendial methods.

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A study of drug response to cisplatin, erlotinib and (E)-2- (4-methoxybenzylidene)-1-benzosuberone in human lung adenocarcinoma

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Background: Lung cancer is the main cause of cancer-related mortality in Hungary. Most of the patients are diagnosed at an advanced stage and referred for chemotherapy. The platinum-based drug, cisplatin still gives the backbone of therapy but in combination with other drugs. Clinical application of targeted therapy e.g. tyrosine kinase inhibitors affecting epidermal growth factor dependent signalling offers better tumour control in the presence of mutation. Chalcones intermediary precursors of flavonoid biosynthesis are also effective against human malignant cells, therefore chalcone analogues could be promising for drug development.

Aims: Our primary aim was to investigate cytotoxity as well as metastasis associated cytokine expression and cellular invasion during mono- and combined administration of cisplatin and erlotinib in human lung adenocarcinomas with known mutations. It was also the aim to study the cytotoxic effect of (E)-2-(4-methoxybenzylidene)-1-benzosuberone in lung adenocarcinoma cell lines.

Methods: Cytotoxic effect of the compounds were tested in primary lung adenocarcinoma derived cell cultures, in 2D monolayer and 3D in vitro cultures using luminescent cell viability assay. Drug-induced changes in mRNA and protein levels were measured by quantitative real-time PCR and cytometric bead array-based assays. For cellular invasions, scratch assays were performed. Cell survival after chalcone treatment was analysed by flow cytometry using 7-AAD staining.

Results: Primary NSCLC derived cell cultures respond to therapeutic drugs similarly in 3D in vitro cultures as detected in clinical therapy. Cisplatin induced an increase in IL-6 and IL-8 cytokine mRNA levels in all patient samples, while erlotinib only increased IL-6 expression in the presence of EGFR mutation. Both cytokine production was increased at mRNA and protein level in EGFR mutant cells in 3D cultures exposed to mono- or combination treatment but erlotinib could reduce cisplatin induced IL-6 protein expression. Cellular migration and proliferation were increased in the presence of IL-6. Cytotoxic effect of the cyclic chalcone analogue and a marked decrease of cyclin D1 proliferation marker expression was detected in a dose-dependent manner.

Conclusion: As the firstly applied drug can determine the clinical response to the second drug, the sequence of drug administration can have a great impact on therapeutic success.

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The investigation of the in vitro penetration of 3 types of model API using modified horizontal diffusion cells

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Background: The nasal administration can be an alternative choice of intravenous intake thanks to the rapid absorption. The residence time and the administered nasal powder dose can be higher than in the liquid formulations. The development of in vitro models can accelerate pharmaceutical development by reducing the resources of the studies. There are numerous diffusion models but they are less suitable for investigating nasal powders [1].

Aims: Our goal was to investigate the in vitro diffusion of different APIs using modified horizontal dif-

fusion cells. 3 types of model APIs were used for this purpose with different hydrophobicity: the hydrophobic meloxicam (MEL, logP = 3.43), the moderately hydrophobic lamotrigine (LAM, logP = 2.50) and the hydrophilic levodopa (LEV, logP = -2.39). The inline results were compared to the offline ones.

Methods: Our setup can be divided into a donor and an acceptor chamber. The offline measurements were performed spectrophotometrically, the inline ones with UV-Vis immersion probe. 3 different membranes and 2 impregnation liquid (isopropil-myristate – IPM and pH=7.4 phosphate buffer) were used (Isopore, Metricel, Whatman). The results of the diffusion studies were analyzed according to the dissolution rate and the arimethric mean of the relative standard deviations (SDmean).

Results: MEL diffusion studies: the inline measurements were more precise than the offline ones. The IPM-impregnated Metricel membrane was the most effective membrane in inline measurements because of the high extent of diffusion and the low SDmean among all setups. LAM diffusion studies: the results of the IPM-impregnated membranes were better-reproducible (low SDmean) in inline measurements. Whatman is suggested based on its high diffusion and high precision. LEV diffusion studies: IPM-soaked Whatman behaved comparable to Metricel but the SDmean in case of Metricel was higher, therefore it is suggested in inline measurements.

Conclusion: Precise inline horizontal setups were constructed to model the in vitro diffusion of model APIs. The hydrophobicity of the API was proportional to the efficient penetration through the IPM-impregnated membrane.

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Effects of acute (S)-ketamine treatment on EEG power spectra

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Background: (S)-ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist with a rapid and long-lasting antidepressant activity. Recently, the U.S. Food and Drug Administration and the European Medicines Agency have approved (S)-ketamine as adjunctive therapy for treatment-resistant depression.

Aims: Most studies have examined the effects of (S)-ketamine on the electroencephalogram (EEG) in anesthetic doses or in a short-term (≤1 h) time scale. Therefore, the aim of our study was to investigate the acute and long-term (≤30 h) effects of the rapid-acting antidepressant (S)-ketamine on EEG spectra.

Methods: Male Wistar rats were equipped with EEG and electromyography (EMG) electrodes. On the day of the experiment, 10 or 30mg/kg (S)-ketamine or 1ml/kg physiological saline was administered intraperitoneally at the beginning of passive phase (at light onset), and EEG, EMG and motor activity were recorded for 30h.

Results: Quantitative EEG (qEEG) analysis revealed that the acutely administered 30mg/kg (S)-ketamine enhanced gamma (30-60Hz) power in the first 3h, and decreased delta (1-4Hz) power in the 2nd h, that was followed by a rebound during passive phase. Both doses reduced alpha (10-13Hz) and theta (5-9Hz) power in the 1st h. In contrast, tendencies to increase alpha and theta frequency band power were observed during active phase, 12-24h post administration.

Conclusion: These findings suggest that (S)-ketamine has a robust effect on gamma activity in the passive phase, and also raise the possibility that subanesthetic doses may have phase-dependent long-term qEEG effects. Future work could involve investigating sleep-wake stage-dependent qEEG effects of (S)-ketamine.

Analytical investigation of organic solvent-free co-grinding technique in terbinafine hydrochloride cyclodextrin complexation

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Background: Recent scientific publications have already demonstrated that co-grinding appears as an efficient, solvent-free technique for preparing cyclodextrin complexes and improving physicochemical properties of active ingredients. Terbinafine hydrochloride (TER), an antifungal BCS II drug was chosen as a model drug, which has poor water-solubility.

Aims: The aim of this study was the analytical characterization of cyclodextrin-TER inclusion complexes prepared by co-grinding used different grinding time (thermoanalytical behaviour, detection of occured changes in crystalline properties, molecular relationships between the components).

Methods: Prospects of preparation and characterization of co-grinded cyclodextrin complexes were studied. TER and amorphous cyclodextrin derivatives (hydroxypropyl-β-cyclodextrin (HPBCD), heptakis(2,6-di-O-methyl)-β-cyclodextrin (DIMEB)) were used for the preparation of products, which were analysed by differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), hot-humidity stage X-ray powder diffractometry (HOT-XRPD), Raman spectroscopy, Fourier transform infrared spectroscopy (FT-IR) and dissolution studies.
Results: Cyclodextrin-TER complexes in the 1:1 molar ratio were prepared. DSC and XRPD studies suggested that crystallinity of products gradually decreased by the increasing grinding time, and after 75 minutes of co-grinding the products were completely amorphous. HOT-XRPD studies revealed that product containing HPBCD remained amorphous with the increasing temperature, while in the case of DIMEB complex recrystallized in a different crystalline phase. Raman and FT-IR spectroscopy were used to confirm the molecular interactions between the components. Dissolution studies showed that dissolution rate of complexes improved, and the solubility of TER increased both in simulated gastric and intestinal fluid, depending on the pH of dissolution medium.
Conclusion: The improvement of solubility and dissolution ratio could enhance the biopharmaceutical properties of the active ingredients in solid pharmaceutical products. Furthermore, stable, amorphous cyclodextrin-containing, organic solvent-free products could be formed efficiently in industrial environment.

High-dose of salicylic acid treatment increases the activity of MMP-2 and 9 in the gastrointestinal and cervical smooth muscle in rats

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Background: Salicylic acid (SA) is a well-known cyclooxygenase enzyme (COX) inhibitor can cause gastric damage and intestinal ulceration already in therapeutic dosage. In our preliminary study, we found that the high-dose of SA induced gastric diverticulum and block of GI passage. Beyond cyclooxygenase enzymes, salicylates may influence the action of other target proteins such as TNFα, NF-κB, PPARγ. The gelatinases like MMP-2 and 9 are expressed in gastrointestinal tract and have an important function in cervical ripening.
Aims: We hypothesized that the GI passage block might be associated with the alteration of activities of MMP-2 and 9. Therefore, the aim of our study was to investigate the effect of high-dose salicylic acid oral treatment on GI smooth muscles motility in vitro and in vivo, and to determine the changing of cervical resistance in rats.
Methods: Non-pregnant female Sprague-Dawley rats were treated to 3 days with high-dose 400 mg/day salicylic acid suspension by oral gavage. The alterations of smooth muscle contractions were determined in GI (intestine, stomach, coecum) and cervical tissues with in vitro isolated organ bath and in vivo electromyography. The activity of MMP-2 and 9 were measured with gelatin zymography and IVIS Lumina imaging system.
Results: After SA treatment, the spontaneous contractions of stomach, ileum and coecum were significantly reduced, furthermore the cervical resistance was also decreased. The intensity of GI electromyographic signal was increased on each day of treatment, the highest values were reached on 2nd day in all samples. Both gelatin zymography and IVIS Lumina imaging system demonstrated that the activity of MMP-2 and 9 were increased by high-dose SA administration.
Conclusion: Our results suggest that the high-dose SA can provoke gastric hypermotility at the start of the treatment while at the end of that, the motility is reduced, and the GI passage is blocked. Furthermore, it can decrease the cervical resistance. It seems that both in GI and cervical tissues the high-dose SA treatment can increase the MMP-2 and 9 activities which may lead to the gastrointestinal and cervical tissues transformation and impaired smooth muscle function.

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Micro- and macrostructural comparison of pH modifier- or solubilizer-containing furosemide-loaded electrospun nanofibers

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Background: Electrospinning technique enables the formulation of novel fibrous drug delivery systems

of improved bioavailability. The selection of proper excipients is the prerequisite of the required functionality-related characteristics of the fibrous system. For this purpose, it is essential to better understand their influence on the fiber formation and functional characteristics of the formulated fibers, including the stability of the drug-loaded electrospun product. Thus an in-depth physical-chemical and morphological study is necessary to define the final composition.

Aims: The present study is focusing on the comparison of solubilizer (triethanolamine) or pH modifier (sodium hydroxide)-containing furosemide-loaded electrospun nanofibers from the point of their micro- and macrostructural properties.

Methods: Two hydroxypropyl cellulose and poly(vinylpyrrolidone)-based formulations were prepared with the addition of triethanolamine or sodium hydroxide to improve the solubility of the furosemide. For the morphological characterisation scanning electron microscopic (SEM) images were performed, and statistical analysis was carried out for the comparison of the distribution of fiber diameters. X-ray diffraction (XRD) spectroscopy and Fourier-transform infrared spectroscopy (FTIR) were applied to investigate the amorphous or crystalline nature of furosemide in the fibrous samples. For further microstructural characterisation positron annihilation lifetime spectroscopy (PALS) was carried out.

Results: The solid-state characterization measurements revealed similar morphology with similar fiber diameter distribution. XRD and FTIR measurements confirmed that the examined formulations contained the furosemide in amorphous salt form, but the PALS measurements indicated different microstructure of the two formulations.

Conclusion: The results may predict different long-term stability features.

Proteomic analysis of human blood derived osteoclast cells

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Background: Osteoclasts have essential role in certain rheumatological inflammatory disorders, however the detailed pathomechaism of these diseases is not yet fully understoodWe have lack of data about the molecular changes during osteoclast differentiation, and the proteome of human blood derived osteoclasts is still unknown.

Aims: Our aims were to optimize a sample preparation and analytical method using nanoHPLC-MS/MS for the proteomic analysis of osteoclasts and their differentiation. After optimizing the methods using healthy samples, we planned to identify and compare the expressed proteins of monocytes, preosteoclasts and osteoclasts; and to determine the differences in osteoclasts proteome of healty population and diseased individuals.

Methods: First, we collect blood samples from healthy donors and isolate monocytes by positive magnetic separation. After this, preosteoclasts and osteoclasts are differentiated from monocytes in vitro using M-CSF and RANK-L growth factors. Next, monocytes, preosteoclast and osteoclast samples are lysed, proteins are reduced, alkylated and digested with trypsin. After C18 clean-up, peptides are separated with nanoHPLC and analyzed with tandem mass spectrometry. The evaulation of raw data is performed using different proteomic databases and softwares.

Results: We have successfully optimized the proteomic sample preparation and analysis on healthy osteoclast samples for maximizing the number of identified proteins and minimizing false positive results. We have determined the proteome of healthy donors' monocytes, preosteoclast, as well as osteoclast samples. Based on our preliminary results there are significant differences among the expressed proteins during osteoclast differentiation.

Conclusion: The developed sample preparation protocol, the applied chromatographic and mass spectrometric conditions, and the properly adjusted evaluation methods are fully appropriate for the analysis of proteomic dynamic changes during osteoclast differentiation. Results obtained with these set methods may promote the better understanding of the molecular pathomechanism of rheumatological diseases.

Antiproliferative and antimetastatic properties of a 17-exo-heterocyclic derivative of androstadiene in vitro

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Background: Cancer is one of the leading causes of death wordwide. Therefore, one of the main goals of

drug research is to find new and effective antitumor molecules. Nowadays, D-ring modified, exo-heterocyclic androstadien analogs are used in cancer therapy (abiraterone). Accordingly, further modifications of this steroid skeleton may result additional effective compounds.

Aims: Our aim was to characterize the anticancer and antimetastatic properties and mechanism of action of 3β-hydroxy-17-[1′-(4′′-cyanophenyl)-4′-hydroxymethyl-1′H-pyrazol-3′-yl]androsta-5,16-diene. Antiproliferative effects of this modified androstadiene derivative have proven in a previous study on human breast cancer cells [1.].

Methods: Antiproliferative effects and tumour selectivity of our test compound were determined by standard MTT-assay on a panel of human gynecological cancer cell lines. Cell cycle disturbances were recorded by flow cytometry after 24h and 48h incubation on SiHa, C33a and MDA-MB-231 cells. Changes in activity of caspase 3 enzyme were detected by a colorimetric assay on SiHa cell line after 24, 48 and 72h treatment. Furthermore, mitochonrial membrane potency of treated and untreated cells were recorded by JC-1 staining. Finally, inhibitory effect of the compound on the early stage of metastasis was investigated by 3D co-culture Circular Chemorepellent Induced Deffects (CCIDs) assay.

Results: Our test compound shows lower IC50 values than 3μM and moderate tumour selectivity compared to cisplatin. Significant changes in the hypodiploid subG1, G1 and S phases and caspase 3 activity were recorded at 2μM and higher concentrations. Therefore, JC-1 staining improved the mitochondrial origin of induced apoptosis. Size of cell –free areas induced by treated tumor spheroids decreased by 30% at 8μM in CCIDs assay.

Conclusion: This study provides experimental evidence that 3β-hydroxy-17-[1′-(4′′-cyanophenyl)-4′-hydroxymethyl-1′H-pyrazol-3′-yl]androsta-5,16-diene has potent antitumor and antimetastatic properties. This compound can be regarded as promising structure in design of new anticancer agents.

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The effect of L-theanine on the D-serine uptake of SH-SY5Y neuroblastoma cells

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Background: D-serine (D-Ser) is a co-agonist of the N-methyl-D-aspartate receptors (NMDAr). Decrease in its extracellular concentration in the brain has been connected to NMDAr hypofunction and the deficit of cognitive functions. Extracellular D-Ser levels in the central nervous system are modulated by neutral amino acid transporters, ASCT1 and ASCT2. L-theanine (L-The), a neutral amino acid and a major component of green tea leaves has been found to improve memory and cognitive functions.

Aims: Our aim was to examine the possible inhibitory effect of L-The on the D-Ser uptake of SH-SY5Y neuroblastoma cells. The cell line has been previously found in our laboratory as a good model of D-Ser uptake into cortical astrocytes.

Methods: Cells were incubated with 25μM of D-Ser and various concentrations of L-The or S-ketamine (S-Ket) for 15min. The intracellular D-Ser concentration was then determined by a capillary electrophoresis laser induced fluorescence detection method. Presence of ASCT1 and ASCT2 in SH-SY5Y cells was confirmed by Western blot.

Results: Although ASCT2 reportedly contributes to a minimal L-The transport, in our experiments L-The significantly inhibited D-Ser uptake into SH-SY5Y cells suspended in Hank's solution. Sixty % inhibition was observed albeit only when high concentration of L-The was used. The experiments were then repeated in cell culture medium abundant in neutral amino acids that are known ligands of the ASC-type transporters. Under this condition a reduced D-Ser uptake was measured possibly due to the competitive effect of these amino acids. L-The was able to significantly inhibit D-Ser uptake even in the medium though only a 22% inhibition was achieved. Having previously described as an inhibitor of ASCT2 we used S-Ket as a positive control. Surprisingly, no inhibition was observed even at several times higher concentrations compared to the previous publication. Its possible long-term regulatory effect on D-Ser uptake was also examined by 72h culturing cells with 25 or 50μM S-Ket. Since no significant change was observed between D-Ser uptake of control and S-Ket-treated cells we concluded that S-Ket does not affect the activity of ASCT1 and ASCT2.

Conclusion: Though reported as an inhibitor, S-Ket failed to inhibit D-Ser uptake or modify the uptake kinetics after a long-term incubation period. L-The, however, was found to be a competitive inhibitor of the ASC-type transporters and it is taken up considerably by SH-SY5Y cells.

Biocompatibility and antimicrobial studies of food and pharmaceutical preservatives

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Background: Preservatives are not highlighted by current scientific research, yet, they are present in everyday life, as their role in the antimicrobial protection of food, drugs and cosmetics is unquestionable. Cheap to use compounds, with a wide range of antimicrobial effect, these chemicals did not change during the last decades, for new molecules applied by industry are few. Publications revealed several limitations in case of preservatives, such as their cytotoxicity, pH dependent inhibitory effect or interaction with other excipients or APIs.
Aims: Our research group is focused on the biocompatibility and antimicrobial investigation of preservatives. Four individual experiments presented at the conference include the structure-activity study of ten p-hydroxybenzoic acid esters; the study of parabens in different complex co-solvent systems; the comparison of sorbates and sorbate esters and formulation of essential oil emulsions as preservatives.
Methods: Our primary technique for assessing cytotoxicity are MTT and NR assays, carried out on Caco-2 human colon adenocarcinoma cell line. In vivo experiments involved *Galleria mellonella* larvae. Antimicrobial tests of different kinds used Candida spp., *E. coli, S. aureus* and *P. aeruginosa* as pathogen model organisms.
Results: Our experiments revealed, that the relative toxicity of parabens is highly modified by the other excipients applied in the product and the non-linear toxicity of the homologous series of parabens. Sorbate esters were more effective against microbes, than sorbic acid and potassium sorbate and the essential oil emulsions proved to be a viable alternative for preservatives.
Conclusion: Innovative compounds and advantageous interactions between preservatives and other excipients are promising new methods for ensuring microbial safety of pharmaceutical products. Meanwhile these new techniques require lower concentrations than the currently recommended molecules which increase their safety.

Risk Assessment based therapy development in cystic Fibrosis

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Background: Cystic Fibrosis (CF) is an autosomal recessive disorder, where the cellular transport's defect results in viscous secretions in different exocrine tissues (respiratory tract, pancreas GI tract, sweat glands, etc). The therapy of this chronic and progressive disorder is complex, lasts a lifetime and significantly influences the Quality of Life (QoL) of patients. The adherence to medical treatment is crucial in this case for the patient's QoL expectations [1]. The Quality by Design (QbD) approach of the pharmaceutical developments is a holistic, systemic, knowledge and Risk Assessment (RA) focused method with profound previous target product design. QbD is a complex process with several steps, by the International Council on Harmonisation (ICH) guidelines and can be applied to each phase of the pharmaceutical research and development and also can be extended [2].
Aims: The aims of this study were the analysis of the early development phase of the pharmaceutical development in CF therapy and the application of the QbD guided risk-based approach in the medicinal product-design by the extended QbD methodology [2] in order to improve patient adherence and quality of life.
Methods: Collection, analysis and summary of all the relevant factors of CF therapy development, with special attention to patient expectations, adherence related factors, therapy and regulatory-specific elements and application of modern quality management tools in visualization, for better evaluation. Implementation of the RA by means of LEAN QbD® Software (QbDWorks LLC, Fremont, USA) in order to determine the factors with most highly risk on therapy development.
Results: After collection, systematization and evaluation of all the therapy-related factors, the RA of the potential critical factors was performed and the ranking of the factors has been determined. Based on the RA results, the recommended intervention points in the CF therapy-management are: increased social support, increased patient education, and increased monitoring.
Conclusion: These interventions stated by the risk-based evaluation of therapy development or management which can improve the patients' quality of life can be the alternative of the costly and time-consuming new drug developments.

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Sleep-wake stage-dependent effects of acute $5HT_{2C}$ receptor antagonist SB242084 treatment on EEG gamma band activity

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Background: Gamma activity of the brain is associated with cognitive and sensory processes and might provide a signature of cognitive state and also network dysfunction. Moreover, alterations of these oscillations have been implicated as biomarkers of depression. On the other hand, several lines of evidence suggest a role of serotonin 2C receptors ($5HT_{2C}Rs$) in the pathomechanism and treatment of depression and anxiety. Numerous drugs used in the therapy of psychiatric disorders, such as most atypical antipsychotics and several antidepressants, possess $5HT_{2C}R$-blocking property. In addition, selective $5HT_{2C}R$-antagonists have been proposed as putative fast-onset antidepressants.
Aims: As we hardly could find any data about the effects of selective 5HT2CR-acting drugs on gamma oscillations in freely moving animals, our aim was to investigate the acute effects of the 5-HT2CR-antagonist SB242048 on the 3060Hz gamma band of the electroencephalogram (EEG) during wakefulness, rapid eye movement (REM) sleep, and non-REM sleep.
Methods: Wistar rats were equipped with EEG and electromyography (EMG) electrodes. Following their recovery and habituation, we administered 1.0mg/kg SB242084 or vehicle intraperitoneally, at light onset (beginning of passive phase), and recorded frontoparietal EEG, EMG and motor activity for the subsequent 3h.
Results: Quantitative EEG analysis performed by means of Fast Fourier transformation revealed that the acutely administered SB242084 markedly enhanced power density in the gamma band (3060 Hz) during non-REM sleep. In contrast, no change was observed during REM sleep and during wakefulness in this frequency band.
Conclusion: These findings indicate that the selective $5HT_{2C}R$-antagonist affected gamma activity, moreover, in a sleep-wake stage-dependent manner (reflecting different brain functions related to gamma oscillations), that may provide further evidence for the therapeutic potential of these compounds in the therapy of depression and/or anxiety.

Formulation and evaluation of BGP15 loaded topical drug delivery systems

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Background: BGP15 is a novel insulin sensitizer drug candidate that also has protective effects in oxidative stress related diseases and may have a protective role in inflammatory diseases.
Aims: The aim of our research was to investigate the anti-inflammatory effect of this molecule by formulating o/w emulsion type ointments, perform biocompatibility assays, check in vitro dissolution of the formulated ointments with the help of Franz diffusion chamber apparatus and formulate nanospheres of the pharmacon.
Methods: Sodium alginate nanospheres were formulated to increase the efficacy of transdermal drug delivery. Formulation has been performed by controlled polimerisation method and the role of the nanospheres has been evaluated. During the formulation we used Büchi B395 Pro Encapsulator. The bead formation is based on the fact that a controlled, laminar liquid jet is broken into equally sized beads, if vibrated at an optimal frequency. To enhance penetration different excipients were incorporated. Since safety is an important case of pharmaceutical formulations, citotoxicity of applied excipients had been evaluated. As in vitro model of human skin, HaCaT cell line was selected. To determine the biocompatibility of these materials MTT cell viability test had been performed. After the ointment formulation membrane diffusion and permeability studies were performed with Franz-diffusion chamber apparatus.
Results: The results of MTT experiments demonstrated that the selected excipients are safe under in vitro conditions. Based on the results of the ointments' dissolution we can conclude that all four compositions resulted very similar dissolution of the pharmacon, so all four surfactants can be used in the future for further investigations.
Conclusion: Based on the results it can be proven that BGP-15 is a versitale molecule and in the future it can be an increadibly useful therapeutic choice for many diseases.

Development and evaluation of ibuprofen rectal gels

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Background: Rectal route represents an alternative to oral administration in pediatrics, a possibility to avoid gastro-intestinal adverse reactions. Ibuprofen is a non-steroidal anti-inflammatory agent, used in all age groups to reduce pain, fever and inflammation.
Our study aims the formulation and characterization of ibuprofen containing rectal gels.
Methods: For the formulation of gels ibuprofen was used as active substance, Carbopol 940, sodium alginate and low viscosity HPMC as gel formers. Propylene-glycol and glycerin were used as permeation enhancers. 5% of ibuprofen was incorporated in all formulations. Three gels have been prepared containing 1 % Carbopol, 0.5 % Carbopol and 5 % HPMC, and 5 % sodium alginate. The influence of formulation variables on the pharmaco-technical parameters were studied: bioadhesion was recorded as the force required to detach the sample from the surface, pH, and diffusion. Diffusion of ibuprofen was measured in phosphate buffer (at a pH of 7.4) with Franz cells. Mathematical models were applied to model the release of active substance.
Results: pH of gels was 4.2-5.0 viscosity varied between 165 and 212 mPas. Detachment force was from 0.02 to 0.12N.
Conclusions: Three gels containing ibuprofen were formulated for rectal used, suitable for children and adults. The obtained experimental results showed a superior release of ibuprofen (10%) from the 5 % sodium alginate gel.

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

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Background: Cyclodextrins are widely used excipients for increasing water solubility, delivery and bioavailability of lipophilic drugs. We showed previously, that cyclodextrins are able to enter Caco-2 intestinal cells by endocytosis, but the different fluorescent labelling has not been compared on the same cyclodextrin derivative. On the other hand, the consequences of the cellular internalization of cyclodextrins have not been revealed yet.
Aims: Our aim was to compare the cellular internalization of fluorescein and rhodamine labelled hydroxypropyl-, (HPBCD) and randomly-methylated-beta-cyclodextrins (RAMEB) and to reveal the appropriate mechanism of the endocytosis. We also wanted to investigate the effects of these derivatives on the NF-κB pathway and autophagy and to examine the involvement of the lysosomal pathway in the cells.
Methods: The endocytosis of the cyclodextrin derivatives was investigated by fluorescence microscopy, the more accurate mechanism of endocytosis was investigated by flow cytomtery using various inhibitors. The effect of cyclodextrins on NF-κB pathway was examined bythe detection of the p65 subunit nuclear translocation by fluorescence microscopy. The effect of cyclodextrins on autophagy was investigated qualitatively by immuno labelling the LC3B molecule in the autophagosomes membrane and quantitatively, whereby the autophagosomes membrane was stained with fluorescent dye. Lysosomes present in Caco-2 cells were examined by fluorescence microscopy and the membrane of the lysosomes was stained by LysoTracker®.
Results: Both fluorescein and rhodamine labeled derivatives are able to enter the intestinal Caco-2 cells by endocytosis. Cooling perfectly inhibited endocytosis, while rottlerin inhibited significantly the uptake. Cyclodextrin pretreatment did not activate the NF-kB pathway. After HPBCD and RAMEB treatments the presence of autophagosomes is detectable, similar to control samples. Using flourescence microscopy we revealed, that these cyclodextrin derivatives are able to enter lysosomes.
Conclusion: 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-κB pathway and does not increase the formation of autophagosomes compared to the control sample. At the same time these derivates can be detected in lysosomes after internalization.

The effect of alpha-lipoic acid on the antitumor effect of bortezomib in melanoma and myeloma cells

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Background: Bortezomib (BOZ) is a proteasome inhib-

itor chemotherapeutic agent utilized to treat multiple myeloma and recently offered to cure melanoma. Bortezomib-induced peripheral neuropathy is one of the most significant and dose-limiting side-effects, which can be treated with antioxidants (e.g. alpha-lipoic acid – ALA and vitamin B_1 – vit B_1) as a part of cancer supportive care. We hypothesized that these antioxidants may counteract the antitumor activity of BOZ.

Aims: The objectives of our experiments were: (i) to verify the cytotoxicity of BOZ; (ii) to test and compare the influence of the antioxidants on the antitumor effect of BOZ in melanoma (A2058) and myeloma (U266) cells as clinically relevant target cells.

Methods: The cell viability was determined by xCELLigence® RTCA SP instrument and by a cell based CellTiter-Glo® Luminescent Cell Viability Assay. Then the possible molecular pattern was characterized by the analysis of phospho-p53 (S15) by flow cytometry and the cell cycle by NucleoCounter ® NC-250™. Cell-based assays were also assessed on the proteasome activity and on the ROS generation.

Results: At first, the cytotoxicity inhibiting effect of alpha-lipoic acid was proved in melanoma cells. Analysis of p53 phosphorylation and the cell cycle progression revealed that ALA failed to counteract the effects of BOZ on these processes. Nevertheless, a good correlation was found between the inhibition of the cytotoxicity, the anti-proteasome activity and the oxidative stress level after the co-treatment with 20ng/mL BOZ + 100μg/mL ALA.

Conclusion: The antagonizing effect of ALA on the antineoplastic activity of BOZ in melanoma cells draw the attention to the proper application of cancer supportive care.

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Characterisation of phenolic profile and antioxidant activity of *Carpinus Betulus*

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Background: Plants are still potential sources of new drugs, however, the ligneous flora is rarely explored in this regard. Hofmann et al. evaluated phenolic compounds and total antioxidant effect of European hornbeam (*Carpinus betulus*) leaf methanol extract [1]. However, analysis of other plant parts has not been performed and diarylheptanoids described in the Betulaceae family, have not been identified in *C. betulus*. Diarylheptanoids have gained interest due to their remarkable anticancer and antioxidant activity [2].

Aims: Our aim was to analyse and compare the phenolic composition of *C. betulus* extracts made from distinct plant parts with various solvents, with special regard to its diarylheptanoid profile. In addition, we aimed to characterise the contribution of individual constituents to the total antioxidant capacity of the extracts.

Methods: Dried bark, leaf, male and female flowers of *C. betulus* were extracted with solvents of increasing polarity (chloroform, ethyl acetate, methanol) in ultrasonic bath. For the phytochemical analyses an LC-ESI-MS/MS method was applied. Diarylheptanoids were isolated by a combination of reversed-phase chromatographic techniques and identified by HR-MS and NMR methods. Total antioxidant activity of the extracts was assayed with the 2,2-diphenyl-1-picrylhydrazyl (DPPH) method. We compared the contribution of each compound to the antioxidant effect against DPPH using an LC-MS method.

Results: Methanol extracts of *C. betulus* were dominated by the presence of gallic acid derivatives and ellagitannins. Ethyl acetate extracts contained gallotannins, hydroxycinnamic acids, flavonol-glycosides and diarylheptanoids. Five diarylheptanoids were isolated from the bark for the first time with carpinontriols A and B being the most abundant. The methanol extract of the leaves showed the highest antioxidant effect, due to its high tannin content. Galloyl-hexahydroxydiphenyl glycosides and other galloyl esters contributed to the greatest extent to the total antioxidant activity.

Conclusion: Phenolic fingerprints of different parts of *C. betulus* were compared and cyclic diarylheptanoids were identified for the first time. Gallotannins were described as constituents being responsible for the antioxidant activity of hornbeam.

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HPLC-DAD-MS investigation of the carotenoid composition of flowers collected in transylvania

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Background: Ethnobotanical studies play an important role worldwide nowadays. The local knowledge of rural people possesses many valuable elements related to drugs of plant origin, such as in the isolated regions in Transylvania, Romania. These field

trips are of pivotal importance to preserve the archaic data, and after comparison with data obtained from scientific databases, plants can be analysed for the phytochemical characters of the ethnomedicinally used parts, e.g. for the carotenoid content of flowers and fruits, as well.

Aims: This paper focuses on the HPLC investigation of the carotenoid composition of flowers of *Telekia speciosa* (heartleaf oxeye, Asteraceae) and six Verbascum species (mullein, also known as velvet plant, Scrophulariaceae), collected in Transylvania, Romania.

Methods: By HPLC-DAD-MS systems based on their UV-VIS and mass spectrum as well as co-chromatography with authentic samples, some main and minor carotenoids were identified in the studied plants.

Results: The flower of *Telekia speciosa* contained lutein as main carotenoid while the minor components seemed mainly carotenoid 5,6-epoxides (neoxanthin, (9Z)-neoxanthin, violaxanthin, antheraxanthin and beta-cryptoxanthin 5,6-epoxide). Carotenes occurred only in traces. In the selected populations some quantitative differences were detected in the identified components. In the flower of Verbascum species lutein and beta-carotene were identified as main compounds. In addition to zeaxanthin, alfa- and beta-cryptoxanthin, alfa-carotene, gama-carotene and delta-carotene were detected. The content of gama- and delta-carotene and their (9Z)-isomers differed significantly (from 3 to 20 %) in the different species. Carotenoid epoxides (except violaxanthin) were detected in traces in the plants.

Conclusion: The yellow flowers usually contain lutein and beta-carotene as main compounds and some epoxides (neoxanthin, violaxanthin) as minor carotenoids. The investigated species show two different but complex carotenoid profils. Unfortunately, at the moment some compounds remained unidentified. The isolation and identification of these compounds are in progress.

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Development and characterisation of solid gastroretentive dosage form based on melt foaming

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Background: Several drugs display site-specific absorption in GI tract. Dosage forms with increased gastric residence time are promising tools to increase bioavailability of drugs with narrow absorption window. Low-density floating formulations could avoid gastric emptying; therefore, sustained drug release can be achieved [1].

Aims: Our aim was to develop a simple, new technology, based on melt-foaming, which can be easily filled into the final dosage form, namely hard gel capsules. After filling, the foam quickly solidifies upon cooling and keeps its structure. Excipients were selected carefully, with the criteria of low gastric irritation, melting range below 70°C and well-known use in oral drug formulations.

Methods: PEG4000, stearic acid, Labrasol and metronidazole were used for experiments. A novel, in-house apparatus was built to mechanically dispersing air into the melt. Densities were determined by the pycnometer method. SEM and MicroCT was performed to characterize the foam and cell structure. Dissolution and floating properties were investigated in pH 1.2 hydrochloric acid media. Dissolution data were also analysed by fitting to kinetic models and by model independent approach. Texture analysis was chosen to monitor the hardness changes of the foams during dissolution.

Results: 53°C was found as an optimal temperature for gas entrapment in the molten dispersion. Stearic acid was necessary to improve the foamability and to achieve density values below 1.0g/mL. The lowest density reached was 0.82g/mL. The cell structure was homogeneous and the smooth outer surface did not form a shell. The shape of the cavities was typically spherical or spheroidal. Cavities formed by the merging of bubbles were present, as well. During the dissolution tests, all samples were proven to possess zero floating lag time. Composition with 10% stearic acid was found to release 86% its drug content in 10 hours. All formulations fitted best to the Korsmeyer-Peppas model and none of them fitted to zero-order or first-order model. Texture analysis confirmed the presence of an unwetted and solid core in the formulation with 10% stearic acid even after 5 hours.

Conclusion: A novel technology was developed to foam hot and molten dispersions on atmospheric pressure, which is applicable to produce floating, low-density moulded dosage forms. Drug was released mainly by the erosion of the foamed matrix.

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A jövő kötelez

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POSTER PRESENTATIONS

Vapor or liquid form? Differences in the antibacterial activity of essential oils against respiratory tract pathogens

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Background: Essential oils (EOs) are complex, volatile substances, which antibacterial application via inhalation is becoming more frequent nowadays. Their antimicrobial potential was confirmed by in vitro methods, which investigated this effect in liquid medium instead of in the vapor phase. In the treatment of respiratory tract infections (RTIs), the patients usually inhale these volatile components. Hence, the investigation of the antibacterial activity of EOs in the vapor phase should be reasonable as well.
Aims: Therefore, our aim was the antibacterial evaluation of clove, cinnamon bark, eucalyptus, thyme, scots pine, peppermint, and citronella oils in liquid medium and vapor phase against respiratory tract pathogens.
Methods: Before the microbiological assays, the EOs were analyzed with GC-MS and GC-FID. The antibacterial activity was tested against *Staphylococcus aureus* (MRSA, 4262), *Pseudomonas aeruginosa* (ATCC 27853), multidrug-resistant *P. aeruginosa* (RPA, 34205), Streptococcus spp., Haemophilus spp., and *Moraxella catarrhalis* (DSM 9143) with macrobroth dilution (BD), and vapor phase (VP) technique. In the BD method, a serial twofold dilution of the EOs was prepared with Polysorbate 80 or DMSO. Four-section Petri dish containing the proper medium was used in VP tests. As a result, the minimum bactericidal concentrations (MBC) and minimum inhibitory concentrations (MIC) were determined. All tests were carried out in triplicate.
Results: Against Haemophilus spp. cinnamon bark oil was the most effective (MIC: 0.06mg/ml) followed by thyme and clove in BD. Clove oil also produced the best inhibition against MRSA (0.1mg/ml). In the case of Streptococci besides cinnamon, clove and thyme produced the lowest MIC in liquid form. In VP test cinnamon bark was the most potent against all investigated pathogens (MIC: 15.62-125µl/l). Besides, thyme, peppermint, and citronella showed activity as well. Eucalyptus and scots pine oil produced moderate activity in our test systems.
Conclusion: On the whole, it should be highlighted that cinnamon, thyme, peppermint, and citronella were effective in both assays; in contrast, clove oil was more effective in the liquid phase. Therefore, they could be promising alternatives to support the treatment of RTIs. We must also note that further studies are required to determine their mode of action and toxicity for their safe application.

In vitro and *in vivo* investigations for the oxidative metabolism of the 4-nitrophenol

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Background: Our experiments were planned to investigate the oxidation of 4-nitrophenol in vivo in physiologic and pathologic (experimental diabetes) conditions, and to test the in vitro oxidation of the compound as well. 4-nitrophenol is mainly excreted to the bile and the small intestinal lumen as its glucuronide and sulfate conjugates, although as a minor metabolite the oxidative 4-nitrocatechol can also appear.
Aims: The investigation and confirmation of applicability of 4-nitrophenol as a model compound to study the activity of the CYP2E1 enzyme through quantitation of 4-nitrocatechol in the small intestinal perfusate and the bile. In vitro oxidation and enzyme activity tests were made for the estimation of the measure of the spontaneous and enzymatic oxidation of the 4-nitrophenol.
Methods: Buffered solution of 4-nitrophenol was recirculated through the proximal segment of the jejunum of a male Wistar rat and samples were collected from the intestinal perfusate and the bile. The samples were quantitated by HPLC method. The enzyme activity was measured from the homogenates of the liver and the small intestine. To estimate the

spontaneous oxidation, the Fenton test was applied. The experimental diabetes was induced by intravenous administration of streptozotocine to rats.

Results: During the measurements, a continuous presence of 4-nitrocatechol was detected in the small intestinal perfusate, while it was undetectable in the bile extracts. The level of the CYP2E1 activity showed an elevation in both the liver and the small intestine.

Conclusion: The performance of the applied analytical method was suitable for quantitation of 4-nitrocatechol and its parent compound. The activity of the CYP2E1 was well measurable and showed an increase in the investigated organs of the hyperglycemic rats. The results of the Fenton tests raise the possibility of the parallel non-enzyme catalyzed oxidation.

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The effect of ethanol on aerosolization properties of spray-dried inhalation powders

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Background: In recent years, near the disintegrating methods, there are three types of integrative processes – spray drying, spray freeze drying, and supercritical fluid technology – for the preparation of dry powder inhalation systems (DPIs). Spray drying is a frequently applied method because of its favorable properties. The use of organic solvents in this process is also widespread, but few publications have investigated how their application to the formulation affects the properties and effectiveness of the formulations using various active ingredients [1, 2].

Aims: The purpose of this work was to investigate spray-dried DPIs of ciprofloxacin hydrochloride (Cip) containing different concentrations of ethanol (EtOH) in the stock solution, to determine how different EtOH concentrations influence the physicochemical and thus aerosolization of the samples.

Methods: Cip was applied as a model drug. The stock solutions contained 0%, 5%, 10%, 20% and 30% EtOH – by the water – under the same production conditions. Particle size distribution, morphology, density, cohesivity, structure was studied in the case of the samples as physical tests. The in vitro aerosolization properties were investigated with the Andersen Cascade Impactor.

Results: The prepared samples were spherical, their average size was less than 5μm, their density was almost the same, and their structural change was similarly compared to the starting drug. However, there was a difference in morphology, with the increase in the percent of used EtOH, more and more dimples appeared on the surface of the particles. Furthermore, the cohesion test also showed differences between the samples. Therefore, the fine particle fraction results showed lower by 5, 10% EtOH and remarkable increase by 30% EtOH compared to the EtOH-free product.

Conclusion: Based on the results, it can be concluded that the mixture of the initial solution solvent used in spray drying – in this case the amount of EtOH used – notable influences the aerosolization results, thus besides the spraying parameters using this investigation is well-founded.

Acknowledgment: This project was supported by the UNKP-19-3-SZTE New National Excellence Program of the Ministry for Innovation and Technology and by the EFOP-3.6.3-VE-KOP-16-2017-00009 project.

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Compounded medicines in oncology care

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Background: Although the selectivity of anticancer treatments has been significantly improved through the appearance of new modern therapies, the management of new types of side effects has become another challenge. Furthermore, conventional chemotherapeutic drugs are still not excluded from therapeutic practice, which almost certainly leads to cell and tissue damage with high proliferative activity. The resulting deterioration in quality of life can be significantly improved by the use of various supportive treatments.

Aims: Some of the side effects of anticancer treatments can be prevented and treated with external topical formulations. Experience has shown that, due to the variety of therapies and the individual differences between patients, the range of factory-made products is not wide enough for the clinic or unaffordable for patients in the long run. Therefore, the use of compounded medicines in individual supportive treatment is widespread. Our goal is to create a collection of prescriptions of external compounded medicines, which are applied and applicable in oncology care.

Methods: We collected the compounded formulations prescribed by our Institute's oncologists from the Novodata software data between November 1, 2018 and October 31, 2019, and compared them with the prescriptions of the standard collection by the

Hospital Pharmacy (Formulae Nosocomiales). In addition, we evaluated which side effects require new formulations. Subsequently, adverse events and related formulations were classified according to the CTCAE classification (similar to the FoNo VII medical edition), indicating which anticancer therapies are expected to occur.
Results: The most common indications are related to side effects on the skin (eg. dry skin, acne, dermatitis, erythema, urticaria, phototoxicity, nail disorders, hand-foot syndrome) and the gastrointestinal mucositis. Ointments, creams and solutions account the largest ratio of applied pharmaceutical forms. It should also be noted that, in the absence of a uniform collection of prescriptions, the formulations proposed by the attending physician show significant variation and prescription errors are common.
Conclusion: A selection of prescriptions helps clinicians, pharmacists and patients manage side effects by making easier to prescribe, to prepare and to redeem the compounded medicine. The uptaking of routine formulations in FoNoVIII should be considered.

In vitro streptozocin treatment: cytotoxicity without alteration in insulin sensitivity

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Background: Alzheimer's disease is a common neurological disorder worldwide with rapidly increasing prevalence. Among several factors cerebral insulin resistance, i.e. the uncoupling of insulin receptor and its downstream signaling pathway has been suggested to contribute to the disease. Therefore, in vivo and in vitro experiments aiming to explore the correlations between neurodegenerative and metabolic disorders are of high importance. In animal and cell culture studies streptozotocin (STZ) is widely used to induce neurodegeneration, however its direct impact on inulin sensitivity of neural cell line has not yet been shown.
Aims: To examine the protective effect of insulin on STZ-induced cytotoxicity and the potential alteration of insulin sensitivity on molecular level in human neuroblastoma cell line.
Methods: The effect of insulin on cell viability and the phosphorylation of glycogen synthase kinase-3 (GSK3) were studied on STZ-treated SHSY5Y cells. Cells of the control group were treated with low serum (LS) medium.
Results: STZ dose-, and time-dependently exerted cellular damage, low, gradual toxicity was induced by 1 mM concentration of the compound. Insulin was found to be similarly cytoprotective in both STZ and LS groups. Also insulin-induced GSK-3 phosphorylation was alike in the STZ and LS treated cells.
Conclusion: According to our results STZ is an appropriate compound to induce slowly developing, non-specific neural toxicity in *in vitro* experiments. However, as insulin showed similar protection and GSK-3 phosphorylation in the LS and STZ groups we can assume that insulin resistance does not play a pivotal role in its action in SHSY5Y neuroblastoma cells, thus it is not a good tool to study the role of insulin resistance in neural death and to study the effect of protective substances that are acting mainly by improving insulin sensitivity.

Antibiofilm effect of pickering nano-emulsion of clove essential oil against *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*

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Background: Biofilms are highly-structured communities of cells that produce an extracellular matrix and adhere to abiotic or biological surfaces, therefore they cause outstanding problems in the health care system. The essential oils (EOs) and their components are becoming increasingly popular in medical applications, because of their proven antibacterial effect. Clove (*Syzygium aromaticum (L.)* Merr. & L.M. Perry) which belongs to the Myrtaceae family is a commercially cultivated tree in tropical and sub-tropical countries. Clove oil is frequently inhaled to prevent respiratory tract diseases or due to its pleasant smell, but evidences are rare related to its mode of actions.
Aims: Our aim was to investigate the biofilm inhibiton effect of clove EO against *Pseudomonas aeruginosa* (ATCC 27853) and *Streptococcus pneumoniae* (DSM 20566). Unfortunately, due to its lipophilic character and low water solubility, the direct use of the EOs, in microbiological experiment is limited.
Methods: Because of this, we prepared O/W type Pickering nano-emulsions stabilized with silica nanoparticles, the nanoparticles were synthesized by Stöber method [1]. Firstly, the MIC [Minimum Inhibitory Concentration] was determined with broth

macrodilution test (*P. aeruginosa*: 1.6mg/mL, *S. pneumoniae*: 0.25mg/mL). The biofilm inhibition experiments were performed on the base of Peeters and coworker's study, with the crystal violet assay [2].

Results: Our results showed that the clove EO had anti-biofilm activity against *P. aeruginosa* and *S. pneumoniae* too, because it reduced the biomass of the bacterial biofilm. It is important to highlight that the Pickering nano-emulsions was more effective (P. aeruginosa inhibitory rate: 76.15%; *S. pneumoniae* inhibitory rate: 66.93%) than the conventional Tween80 stabilized emulsions (*P. aeruginosa* inhibitory rate: 69.23%; *S. pneumoniae* inhibitory rate: 60.77%).

Conclusion: In this study, the antibiofilm effect clove EO was investigated against *P. aeruginosa* and *S. pneumoniae*. We can conclude that O/W type Pickering nano-emulsions of clove EO provide a new possibility for biofilm inhibition.

Support: This work was supported by Development and Innovation Office and the European Union co-financed by the European Social Fund (EFOP-3.6.1.-16-2016-00004). Gy. Horváth was supported by the NKFI 18 K 128217 grant.

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Practices of portable and disposable, elastomeric pump use in oncology care

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Background: Administration time of cytostatic infusions can vary in cancer care, it can be one or two days regarding the therapy. Because of limited capacity of oncology departments and patients' preference, there is an opportunity to administer chemotherapy by a portable and single-use elastomeric pump, which infuses the medication at a controlled flow rate over the prescribed amount of time. Therefore, it isn't obligatory for the patients to stay in the hospital. However inadequate use of elastomeric pumps may increase the risk of adverse events.

Aims: The preparation of cytostatic infusions is centralized in our institute and done under pharmacist surveillance. We experienced an increased need for portable, elastomeric infusion pumps with the active ingredient 5-fluorouracil at our oncology departments. Our goal is to review the national and international practices of pump use and related patient education if it's provided.

Methods: We created an anonymized questionnaire in Hungarian and English, which was sent to 35 Hungarian oncology departments' clinical pharmacists and to 60 member countries' ESOP (European Society of Oncology Pharmacy) delegates as well. Beyond the general questions about the capacity of the oncology departments, we asked about whether the patients receive education about the portable, disposable elastomeric infusion pump and if yes, is it in written or verbal form, who is it performed by, and what topics are included.

Results: We received 17 answers from Hungary, and 7 from foreign countries, which are more or less similar in one way and different in others. Answers came from universities and general hospitals as well, therefore the reported capacity and the number of the elastomeric pumps used by month shows differences. Many institutes experienced an increasing tendency of elastomeric pump use in the recent years, similarly to our situation. It's a positive result that patients receive education, but it is not comprehensive at every site, and it is rarely written. The education should point out not just how to change the daily routine but the danger of contamination too. It is also an important fact, that in the elastomeric pump the active ingredient is not as much diluted as in an infusion, so thrombophlebitis may occur more often.

Conclusion: In summary, the fact is that portable and disposable elastomeric pumps are widely used and part of everyday practice, therefore this should be followed by proper patient education. With this questionnaire hopefully, more institutions' attention will be raised to this topic and a patient education material might be introduced about the use of elastomeric pump.

Potentiation of the uterus relaxing effects of magnesium-sulfate with terbutaline and nifedipine: studies on pregnant rat myometrium

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Background: Tocolysis is one of the greatest challenges in obstetrical practice. Magnesium-sulfate ($MgSO_4$) is an expansively used tocolytic agent, as it has better side-effect profile compared to other agents. However, the efficacy of this drug has been questioned.

Aims: Our aim was to investigate the uterus-relaxing effect of magnesium-sulfate in combination with other tocolytic drugs in vitro and in vivo.

Methods: Contractions of uterine rings from 22-day-pregnant Sprague-Dawley rats were measured in an organ bath. The contractions were stimulated with 25mM KCl and cumulative-dose response curves were elicited in the presence of $MgSO_4$ (10^{-8}–10^{-1}M), nifedipine (10^{-10}–10^{-6}M) or terbutaline (10^{-9}–10^{-5}M). The uterus relaxing effects of nifedipine and terbuta-

line were also investigated in the presence of magnesium-sulfate (10^{-7}M). The in vivo studies electromyographic studies were carried out during ketamine (36mg/kg) and xylazine (4mg/kg) induced anesthesia with the subcutaneous implantation of and electrode pair. The rats were treated with 10mg/kg $MgSO_4$ intravenously, then 0.05-0.15-0.5-1.5-5-15-50μg/kg terbutaline or 0.05-0.15-0.5-1.5-5-15-50μg/kg nifedipine were given in cumulative bolus injection.

Results: Both terbutaline and nifedipine caused myometrial relaxation in vitro, which was further enhanced by administration of $MgSO_4$. The $MgSO_4$ increased the maximal relaxing effect of terbutaline ($p \leq 0.001$), while it shifted the dose-response curve of nifedipine to the left ($p \leq 0.5$). In the in vivo studies $MgSO_4$ increased the uterus-relaxing effect of terbutaline, however it could not enhance the effect of nifedipine.

Conclusion: The combination of $MgSO_4$ and terbutaline may have a clinical significance, that must be justified in clinical trials. Additionally, this combination is supported by the fact that the pharmacodynamic, pharmacokinetic parameters and risks of these two agents are well-known separately. However, the combination of magnesium-sulfate and nifedipine may have not any therapeutic benefit. We suppose that $MgSO_4$ closes the voltage dependent Ca^{2+}-channels and therefore could not potentiate the effect of nifedipine.

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Model development for assessing cost-effectiveness and prepare reimbursement dossier of RTMS in patient population with treatment-resistant depression in hungary

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Background: Major depressive disorder (MDD) is a common mental illness as being the second leading cause of disability worldwide. Treatment-resistant depression (TRD) amounts to 45% of total MDDs, however the definition is not yet standardized. Repetitive Transcranial Magnetic Stimulation (rTMS) has a rich literature for the treatment of TRD-patients.

Aims: The aim of this study was to define an appropriate model concept for the cost effectiveness analysis of rTMS intervention in the TRD subpopulation of MDD in Hungary from payer perspective, to support the reimbursement process initiated by a tertiary healthcare provider.

Methods: A systematic literature review was conducted and reported in compliance with the PRISMA Statement. After the screening, potentially relevant articles were analyzed in full text, and data were systematically extracted by use of explicit methodology.

Results: The search query resulted in 61 articles, which after the deduplication and title abstract screening were narrowed down to six from which information about models employed in full economic analyses of rTMS were extracted. In general, within these articles a model time equal or shorter than 1 year were applied to cover the acute phase and a short maintenance period, however no relapse was implemented due to short model time. From methodological perspective decision tree and Markov models were used to assess the effect of rTMS during the acute and maintenance phase respectively. TMS provided a net cost saving of US$1123 per QALY when compared with the current standard of care [1].

Conclusion: Based on the identified conceptual challenges we developed a model in line with the HTA guideline of Hungary. The model applies the combination of decision tree in the acute and Markov model in the maintenance phase with medical management as comparator. The suggested model time is 3 years, which enables to model relapse, aligned with the natural history of the disease.

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The influence of the suboptimal body mass index (BMI) on the use of healthcare resources in post-surgical patients: a clinical database study

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Background: Malnutrition is associated with higher complication rates and increased hospital costs. Electronic Medical Record (EMR) systems collect large amounts of data, which were made accessible for research purposes after pseudonymisation. This is a pilot study in a project addressing the secondary use of clinical data asset of our institution.

Aims: Our goal is to determine the impact of malnutrition, as measured by the Body Mass Index (BMI), on healthcare resource utilization in surgical patients using EMR data collected in our Medical Center.

Methods: Relevant patient data was extracted from the hospital information system, rearranged, and transformed to the goals of the study. Study population consisted of adult inpatients who underwent surgery between November 2016 and August 2018, had no previous surgery within 30 days, and for whom a preoperative BMI score was available. The duration of hospitalization after surgery, the number of readmissions within 30 days, and the number of outpatient visit up to 30 days after hospitalization were analyzed in patients with low (<18.5, n=137) and normal (18.5-26, n=1904) preoperative BMI by linear regression analysis.
Results: The mean age of the low BMI group was 52.2 years compared to 61.03 ($p < 0.001$) of normal group. The proportion of women in the low and normal BMI group was 66.4% and 55.7%, respectively ($p < 0.05$). Using a simple linear regression model, the average length of stay in the low BMI group was 1.4093 days longer ($p = 0.0129$), while after controlling for age, gender and ICD codes the difference increased to 1.6002 ($p = 0.005$). However, the preoperative BMI showed no significant effect on the other two variables observed.
Conclusion: The results suggest that after data transformation of EMR useful information on patient risk factors can be retrieved. Even with such a simple indicator as BMI, the impact of malnutrition on patient outcomes can be quantified. Even though, further studies on the applicability and generalizability of this method, using more data from a wider range of healthcare providers are needed, nutrition therapy indicated by clinical pharmacist may lead to reduction of healthcare resource use.

Current practice of online drug distribution in Europe – a panoramic view of the internet pharmacy markets of the eu member states

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Background: Since the launch of the first European internet pharmacy, member states have adopted different national regulations on online pharmacy services and the dispensing of drugs over the Internet. EU and national authorities recognised the potential threats associated with the illegal internet pharmacy market. Five years ago the European Commission adopted the common logo for legally operating online pharmacies and member states are required to develop and maintain a register of all legal online drug stores.
Aims: The aim of this study was to provide an overview of these public registers of national medicines authorities and summarize the current landscape of the European internet pharmacy market.
Methods: Based on the existing regulations of Directive 2011/62/EU, we collected the publicly available information related to each member state from national authority websites like the number of internet pharmacies, community pharmacies, inhabitants, and territory of the states and the legally tradeable product range. European Commission documents and EU case law databases were reviewed to determine whether infringement procedures had been initiated in connection with the relevant obligations in the Directive.
Results: Only 21 of the 28 states (77.8%) have publicly available registries for legitimate online sellers. In 14 states (50%) only OTC products are tradeable; 7 states (25%) were found where both OTC and POM can be distributed; in 3 countries (10.7%) POM can be distributed only with restrictions and in 4 countries (14.3%) no information was found related to tradeable products. The research had found that save for some infringement procedures started by the European Commission for late implementation, no substantive infringement of the Directive had been ascertained; these infringement procedures were also resolved without a Court procedure.
Conclusion: The online distribution of medicines has undergone tremendous change in the past and is still in the process of shaping. The current results show that compliance with the regulations is not complete and shows some difficulties in practice. The European online pharmaceutical market is complex due to member states' different legislative, pricing and reimbursement backgrounds. A unified formal requirement or recommendation adopted at the EU level could make it easier for Member State authorities to fulfill their obligation regarding the public registry of online retailers.

Prevalence and antibacterial resistance among predominant bacteria

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Background: Antibacterial resistance is one of the most important threats to public health. The knowl-

edge of local epidemiology and resistance patterns are essential for antibacterial stewardship programs.
Aims: To map the prevalence, the source and bacterial resistance profile of predominant bacterial isolates.
Methods: The study was performed at the level I Emergency Department of University of Szeged. Data on positive microbiological isolates were retrieved for the period between 1st July 2014 and 1st July 2019. Duplicate isolates were removed. Bacterial identification was performed using MALDI-TOF MS. Antibiotic susceptibility-testing, phenotypic detection of resistance mechanisms and interpretation of drug resistance (MDR/XDR) categories were based on ESCMID/EUCAST standards.
Results: Overall 6887 bacterial isolates were recovered of which 66.7% were Gram-negative species. The most frequent clinical specimens were blood culture (35.6%), urinary catheter (23.1%), midstream urine (12.1%) or deep wound or abscess samples (14.0%). *Escherichia coli* was the most frequent Gram negative isolate (2191), followed by members of the Klebsiella genus (664, most frequently *K. pneumoniae*) and the Proteus spp. (526, most frequently *P. mirabilis*). Among Gram-positives, the most frequent isolate was *Staphylococcus aureus* (561) and Enterococcus spp. (471). The top five bacterial family/species accounted for nearly 65% of positive clinical isolates. The resistance of *E.coli* and *K. pneumoniae* for penicillin combinations (with beta-lactamase inhibitors) and different cephalosporins ranged between 13.3% and 18.2 % and 23.4% and 32.5%, respectively, while ciprofloxacin-resistance level exceeded 30% for both species. Similar resistance profile was shown for *P. mirabilis*. Methicillin-resistant *S. aureus* (MRSA) was detected in 16.1%, while vancomycin-resistant *E. faecium* was detected in 33.3% of isolates overall.
Conclusion: We identified the most frequent bacteria and revealed the current resistance patterns of bacterial isolates. Some of the data (e.g. fluoroquinolone resistance) raises concerns that may pose therapeutic challenges in the most frequently isolated bacteria. These results should be taken into consideration when updating local antimicrobial guidelines.

Teicoplanin and vancomycin derivatives with perfluorilated alkyl groups are active against influenza and coronavirus

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Background: As we have seen in the last six months, emerging and re-emerging viruses could be the biggest threat for the human population nowadays in our modern, accelerated and globalized world. Both of influenza and coronaviruses have the potential to cause serious pandemics worldwide. Unfortunately, there are no effective enough medications against most of these viruses.
Aims: As some glycopeptide antibiotics and their derivatives proved to be effective against several viruses1, therefore we planned to synthesize some new derivatives equipped with highly fluorinated lipophilic groups.
Methods: Perfluorobutyl and perfluorooctyl groups were conjugated to the N-terminus of teicoplanin pseudoaglycone and vancomycin aglycone derivatives through ethylene glycol and tetraethylene glycol linkers by means of photoinitiated addition and azide-alkyne click reaction. The effect of the derivatives were evaluated against several viruses including influenza and human coronavirus.
Results: Vancomycin aglycone derivatives were inactive against all of the studied influenza strains, while 3 out of the 4 perfluorobutyl and perfluorooctyl derivatives of teicoplanin pseudoaglycone displayed very good activity against influenza H1N1, H3N2 and B strains. Two of the derivatives were active against human coronavirus as well.
Conclusion: We hope that these results can open a new way in finding more effective antivirals based on glycopeptide antibiotics.

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The influence of stearic acid in water removable cream bases with moisturizing properties

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Background: Water removable bases are oil-in-water cream bases and there are the most used types of

creams because they have a texture nongreasy and therefore aesthetically pleasing.
Aims: Our study aims the formulation and characterization 4 types of bases with Polyglyceryl-3-methylglucose distearate (PGMGds) as emulsier and stearic acid in different concentration
Methods: Cream bases were manufactured using the following componets: PGMGds, Olea Europaea Fruit Oil cold pressed, stearic acid, cetyl palmitate and distilled water. The emulsions were prepared by using different methods and and their stability was determined. Pharmacotechnical parameters and skin moisture level were studied [1,2].
Results: pH of creams was between 5.70-7.40. The thixotropy is emphasized in all the formulas, making exception the last formulation who has the highest consistency with contain the maximum quantity of stearic acid and PGMGds. The addition of 1% stearic acid causes the pH to decrease by 0.8 units (5.7 – 6.5), without affecting the adhesion (which is kept at 0.0016 N/mm^2); The first formulation which contain the minimum quantity of stearic acid shows the highest increase in hydration level 4 hours after a single application. All types of thease cream bases have a very good stability in different types of preparing.
Conclusion: According to the pharmacotechnical analysis performed the most optimal formula contain 3-3.5% PGMGds and stearic acid 3%. If the formula contains 3% PGMGds and stearic acid 4% the pharmacotechnical analysis are performed but the moisturizing is very lower. The formulas that has all the desired characteristics are those with contain only 3% stearic acid.

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Off-label in neonatology – creative therapy solutions

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Background: Off-label drug use (use of medicines other than in the summary of product characteristics [SmPC]) is considerable in the pediatrics, as special in neonatology.
Aims: Investigation of the reasons for various therapies used in neonatological practice.
Methods: Relevant literature research in databases (Pubmed, Cochrane, Uptodate).
Results: Paracetamol is suitable for close the patent ductus arteriosus (PDA) and the quality of evidence is moderate. It inhibits prostaglandin synthesis. Its side-effect profile is more favorable than that of ibuprofen, and paraceramol has the same efficacy as ibuprofen and indomethacin. There is no difference from ibuprofen in neurodevelopmental outcome, but the evidence for this is low, and in view of concerns after prenatal and postnatal exposure of paracetamol 18-24 months' postnatal follow-up should be required [1]. In the treatment of neonatal sepsis and necrotizing enterocolitis (NEC), intravenous pentoxifylline may be an adjuvant therapy in addition to antibiotics. Pentoxifylline is a phosphodiesterase inhibitor and it suppresses TNF-α production, thereby reducing inflammation, tissue damage, and has a positive effect on endothelial cell function and coagulation. With low-quality evidence, in combination with antibiotics, it reduces mortality and length of hospital stay for newborn sepsis. No adverse effects were identified. Further better quality evidence and studies are needed to support its use in NEC [2]. Recombinant human erythropoietin has promising neuroprotective effects. In a meta-analysis, prophylactic erythropoietin improved cognitive development, reduced the incidence of mental developmental index (MDI) <70 in infants, but had no effect on other neurodevelopmental outcomes. Further controlled, randomized trials are needed to schedule and dose the treatment adequately [3].
Conclusion: Off-label therapies can help the recovery, but the evidence of effectiveness is moderate or low, and further studies are needed to assess their efficacy and safety.

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Development and evaluation of amlodipine/ atorvastatin immediate release tablets

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Background: Increased blood pressure and dyslipidemia are two diseases which can be found associated in elderly patients. The association of two active ingredients in one tablet can increase the patient's compliance.
Aims: This study aims in developing and evaluation of new formulation of tablets with a content of amlodipine besylate (AB) and atorvastatin (AT) (10/10mg).
Methods: In this study were developed 3 formulations FI, FII and FIII in which the concentration of ac-

tive ingredient, disintegrant (pregelatinized starch) and lubricant (colloidal silicon dioxide) were maintained constant; the quantity of the diluent (microcrystalline cellulose) and the association between the superdisintegrants (croscarmellose sodium-CCS and sodium starch glycolate-SSG) has been varied. The tablets were prepared by direct compression having a 10mm diameter. The following pharmacotechnical properties were evaluated: variation of mass, friability, mechanical hardness and disintegration time. The releasing study of the two APIs was realized in phosphate buffer (pH6.8). The concentration of AB and AT were determined spectrophotometrically.

Results: For the proposed formulations, uniformity of mass showed a deviation by the average mass less than 5% and the friability was less than 1%. The results of the disintegration test depended on the type and concentration of superdisintegrant. The superdisintegrant determined a twice lower mechanical resistance compared with FI formulation. The lack of superdisintegrant in FI formulation conducts in a released concentration of 79.49% AB after 30 minutes and 82.18% AT after 60 minutes. The presence of sodium croscarmellose determined a released concentration of 67.89% AB after 40 minutes and 86.49% AT after 25 minutes. The use of sodium starch glycolate determined a released concentration of 79.58% AB after 35 minutes and 96.87% atorvastatin after 45 minutes.

Conclusion: Pharmacotechnical properties of the three formulations are in the range limits provided European Pharmacopoeia 8th Edition. The release of AB and AT from the 3 formulations is directly corelated with the presence/absence of the superdisintegrant, but not with the type of the superdisintegrant used.

Utilization of lipid modifying medications in Hungary between 2008 and 2018

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Background: Morbidity and mortality rate of cardiovascular diseases are very high in Hungary and lipid lowering drugs have an important role in prevention and treatment.

Aims: Our aim was to analyse the trends of lipid modifying agents use focusing on statin utilization in Hungary between the period of 2008 and 2018.

Methods: Reimbursed national drug utilization data for the entire population of Hungary were obtained from the National Health Insurance Fund. Data were analysed using the WHO's ATC/DDD system and were expressed in Defined Daily Dose per 1000 inhabitants per day (DDD/TID), and in percentage of the total use.

Results: The use of lipid lowering agents (ATC: C10) grew from 69.7 DDD/TID in 2008 to 110.1 DDD/TID in 2018. 91.2% of the total use was statins (also including combination products) and 6.4% of the total use was fibrates and 2.4% of the total use was ezetimibe in 2018. During the study period the statin use was emerging, 87.2% of the total use was statin monocomponent products (95.9 DDD/TID) and 3.9% of the total use was combined statin products, mainly atorvastatin or rosuvastatin with amlodipine (4.4 DDD/TID) in 2018. While in 2008 the most consumed drug was atorvastatin, rosuvastatin has showed a growth and overtook atorvastatin use by 2014. These two agents accounted for 94.0% of total statin use in 2018.

Conclusion: Lipid modifying drug use considerably grew, and statin use was the highest throughout the 11-year study period.

Possibility of an anti-adhesion based therapy and prophylaxis in the treatment of pseudomonas aeruginosa infection

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Background: Lectins are specific carbohydrate-binding proteins of a non-immune origin. Lectins could be important virulence factors, involved in recognition and adhesion processes, moreover promising therapeutic targets which could be inhibited by carbohydrate ligands. Lectins are usually multimeric proteins, containing several binding sites per molecule and/or forming oligomers. Consequently, the multivalent carbohydrate moieties are considered to be potential drugs for anti-adhesion therapy [1]. The Gram-negative bacterium P. aeruginosa (PA) is an important opportunistic pathogen, it produces soluble, galactose-specific lectin PA-IL [2]. Specifically, PA-IL displays toxicity to respiratory epithelial cells in primary culture. Due to its importance, several multivalent inhibitors were designed and tested against PA-IL.

Aims: The aim of this research was to synthesize oligovalent D-galactose presenting glycoclusters via click-strategy and the potency of glycomimetics with lectin PA-IL was investigated.

Methods: The methods of classical organic chemistry, mainly the azide-alkyne click-reaction was used

for the syntheses. The interaction of glycomimetics with lectin PA-IL was examined by biophysical methods. Inhibition of PA (isolated from a cystic fibrosis patient) adhesion to epithelial bronchial cells was tested by ex vivo bacterial adherence assay.

Results: Novel tetravalent galactose-presenting ligands were synthesized, biophysical assays proved that all compounds were suitable ligands of the lectin in vitro, with significantly better inhibitory effect than simple galactose. Two candidates were able to decrease adhesion of PA cells to bronchial human cells in the ex vivo adhesion assay.

Conclusion: The anti-adhesion therapy with glycomimetics and the application of multivalent glycoclusters might be novel tools and supporting methods in the treatment of P. aeruginosa infection. In conclusion, some ligands are promising candidates for testing using a mouse cystic fibrosis model with potential future utilization as prophylactic agents against bacterial colonization of lungs.

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Antioxidant and antimicrobial investigation of *Lysimachia Nummularia L.* applied in the Transylvanian Ethnomedicine

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Background: In folk medicine in Transylvania several plants are used nowadays frequently mentioned for skin problems.

Aims: Based on our earlier collection, among plants applied for wounds, *Lysimachia nummularia* was selected for antioxidant and antimicrobial tests.

Methods: Plant extracts were prepared by methanol, hexane, chloroform, ethyl acetate, butanol and water according to Lee et al. (2014). Mueller-Hinton broth and agar were used for microdilution methods and evaluation of minimum inhibitory and bactericidal concentration. Tested strains were the following: *Staphylococcus aureus* ATCC 23923, MRSA ATCC 700698, *Escherichia coli* ATCC 25922, *E. coli* ESBL, *Klebsiella pneumoniae* ATCC 13883, *K. pneumoniae* ESBL, *Pseudomonas aeruginosa* ATCC 27853, *P. aeruginosa* MDR, *Salmonella typhimurium* ATCC 14028, and *Acinetobacter baumannii* MDR. Enhanced chemiluminescence (ECL), Oxygen Radical Absorbance Capacity (ORAC), 2,2-diphenyl-1-picrylhydrazyl (DPPH), and Trolox Equivalent Antioxidant Capacity (TEAC) assays were used for the study of antioxidant potential of ethanolic and water extract of the plant (Kőszegi et al. 2017). In ECL and ORAC tests, results were calculated by the calibration curve using the net area under curve based on Trolox dilutions. The total antioxidant activity was given as Trolox equivalent referred to 1 g (in μmol/g). In DPPH and TEAC tests, radical scavenging activity was expressed as the inhibitory concentration at 50% (IC50; in μg/mL), which was calculated by a linear regression analysis of % scavenger activity.

Results: In the microbiological study, methanol and butanol extracts showed inhibition on E. coli ATCC 25922, both *K. pneumoniae* strains, MRSA, and *S. aureus*. Hexane and ethyl acetate extracts were effective in the lowest concentration against *S. aureus* and MRSA. Water extract had antimicrobial activity against each strain except for *P. aeruginosa* and *A. baumannii* which were not inhibited by any tested phases. In antioxidant tests, ethanolic extract showed higher total antioxidant capacity than water extract in each assay, which can be related to the higher polyphenol content in ethanolic phase.

Conclusion: Our preliminary data give new records for *L. nummularia* which will be further analysed for phytochemical profile and medicinal use.

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Effect of particle size on dissolution: a study on micro- and nanosized drugs

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Background: The bioavability of a drug is largely determined by the physico-chemical properties of the active ingredient. Among these, the solubility, the rate of dissolution and the membrane permeability are the most important ones. Poor solubility, low dissolution rate and poor permeability may result in improper absorption. Is it known, that the particle size of a compound or the different excipients can influence the dissolution rate.

Aims: The aim of this study was to investigate the equilibrium solubility and the dissolution kinetics of different model compounds under in vitro conditions. We also conducted measurements in a biomimetic medium. The selected active compounds were available in macro crystalline, micronized, and nanonized (with various excipients) forms, thus ena-

bling the study of the role of particle size on the dissolution kinetics.
Methods: The equilibrium solubility of the drugs was determined using the saturated shake-flask method, where the concentration of the supernatant was measured by spectroscopy using a Jasco V-550 UV/VIS spectrophotometer. In-situ UV probes were used to monitor the dissolution in real-time, so it was possible to obtain precise information on the time needed to achieve the equilibrium, and the rate of supersaturation.
Results: Measurements were performed using different solvents: stimulated gastric fluid (SGF), fasted state simulated intestine fluid (FaSSIF), fed state simulated intestine fluid (FeSSIF) and the blank buffers (FaSSIF blank and FeSSIF blank). In the case of macrocrystalline and microsized drugs the measurements were performed in the presence of the excipients used at the nanonized drugs, so we can eliminate their effect on the solubility and the dissolution.
Conclusion: Our results show that the particle size can influence the dissolution of a drug. Nanonized drugs reach the highest concentrations, but the solubility and the dissolution of the micronized drugs were also better than the macrocrystalline forms. We observed that in most cases the excipients used by us did not have a solubility increasing role.

Synthesis and evaluation of quinoline photocages with improved aqueous solubility

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Background: Photolabile protecting groups ('photocages') allow the temporary inactivation/masking of biologically active agents and their subsequent spatiotemporally controlled re-activation upon light irradiation (UV – one-photon or NIR – two-photon) via cleavage of the blocking group. Appropriate photolabile moieties open up several potential experimental and eventual therapeutic applications. Of the various photocage families described in the literature, quinolines being synthetically available and having interesting one- and two-photon uncaging quantum yields were selected as core protecting group scaffolds [1-3].
Aims: For biological applications, photocages should comply with several criteria [4]. In particular, photocages should be reasonably water-soluble (ideally at least in the 50-100mM range), a real challenge as typically chromophores favoring two-photon absorption are characterised with extended conjugation, therefore higher lypophilicity. In the present study we assessed structural modifications for improving this critical aspect. Several small-molecule quinoline cages were studied with various substituent patterns previously. In the present work we set out to prepare novel derivatives with substituents confering better aqueous solubility without hampering the uncaging efficiency.
Methods: A novel set of quinoline photocages were prepared using palladium-catalysed coupling or N-alkylation reactions and further side chain functionalisations. The novel photocages were characterised by standard methods for one- and two-photon uncaging quantum yield, fluorescence, UV-absorption, aqueous solubility and stability.
Results: Synthetic pathways for a small library of novel quinoline photocages were developed. A comparative study of aqueous solubility was accomplished using both computational and experimental methods.
Conclusion: The effect of modifications with various hydrophilic substituents on the photophysical and photochemical properties was evaluated on a small set of quinolines, helping the design of future improved photocages.

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Treatment of obesity in pharmaceutical care

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Background: Obesity – which is not only a Hungarian, but also a world phenomenon – puts the appearance of some serious diseases at high risk, such as intense heart muscle load, hypertension, diabetes, atherosclerosis, gall diseases, musculoskeletal system diseases, sleep apnea, tumor.
Aims: There are possibilities to direct patients in the direction of a healthier way of life within the confines of pharmaceutical consultation. We offer the Premium Diet program, a long and continuous diet, which together with the necessary exercises treats obesity. Mental health control, regular consultation are also extremely important.
Methods: At the start of each nursing consultation process the following measurements take place: body weight, abdomen circumference and blood pressure, blood sugar level, cholesterol level and triglycerides level. With the help of a BIA instrument body cell weight, extracellular liquid, fat weight, fat-

less weight and hydration values are also determined. After these measurements a consultation query is filled out – target weight, use of the formulas, full value lunches, the necessary exercise and the consultation appointments are discussed. The district doctor of the patient is advised of the patient's involvement in this program, with special attention to the proper drug administration.
Results: Based on the results of the measurements it can be said that significant body weight decrease (10-24%) is always accompanied by great amount of fat reduction and abdomen circumference decrease. The determined values were found in the normal range. It is important to mention that during the diet the patients hadn't reported any negative mental effects. The Premium products are suitable for body weight and body fat reduction without the reduction of the skeletal muscles.
Conclusion: The results of the diet with the Premium program has clearly convinced us that by losing weight, applying appropriate diet and customized exercising patients can be helped fighting overweight. Moreover, diseases in connection with obesity can also be improved this way. The new available instrument gives us the possibility to make pharmaceutical consultation even more comprehensive.

Opioid utilisation in Hungary between 2006 and 2019

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Background: Analgesia is a fundamental human right and an extremely important task in patient care. Severe pain can be successfully treated with opioid analgesics. In ambulatory care, the main indications for opioid drug prescriptions are cancer and musculoskeletal pain.
Aims: To gain comprehensive knowledge on the national opioid utilisation trends in ambulatory care over the last 14 years in Hungary.
Methods: Raw national drug utilization data on reimbursed medicine for the entire population of Hungary were obtained from the National Health Insurance Fund. The study period was set from 2006 to 2019. The data were analysed using WHO's ATC/DDD system and were expressed in DDD per 1000 inhabitants per day (2020 version). We focused our analysis on the N02A ATC subgroup.
Results: During the study period, there was a monotonic increase in opioid use from 3.05 DDD per 1000 inhabitants per day in 2006 to 5.09 DDD per 1000 inhabitants per day in 2019. Tramadol and tramadol combination prescriptions steadily covered approximately 75% of the opioid use throughout the study period. Fentanyl products were the second most prescribed opioids while other opioid drugs (oxycodone, codeine, dihydrocodeine, hydromorphone, morphine, buprenorphine) amounted to less than 10% of dispensation. There was an increase (0.02 vs. 0.29) in fentanyl use in the indication-linked 90% reimbursement category, which means that musculoskeletal pain is becoming a more and more frequent indication. Increase in the consumption of 25μg/h fentanyl patches also supports this assumption since that is the most potent patch that can be prescribed for musculoskeletal pain. In the final year, the amount of prescriptions in this reimbursement category was more than half of the amount of prescriptions in the category of cancer pain management.
Conclusion: Opioid utilisation gradually increased over the last 14 years in Hungary. Tramadol consumption was persistently dominant, with an increase in the use of combinations.

First steps of introducing antimicrobial stewardship

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Background: Spreading of antibiotic resistance of pathogens is a real problem not only in Hungary, but in most parts of Europe as well, in the emergence of which irresponsible or nontargeted use of antibiotics plays a crucial role. Continuous monitoring of the use of antibiotics in inpatient care facilities is also governed by regulations to restrain this problem. Since September 2019, also an Antibiotic Stewardship (ABS) Team has been operating in Petz Aladár County Teaching Hospital based on the Methodological Guideline for Antimicrobial Stewardship in Inpatient Care Facilities. Our opportunities are seriously limited by the fact that we currently have enough professionals with adequate qualification for the setting up of only one ABS.
Aims: In the 1438 bedded Petz Aladár County Teaching Hospital, clinical audits of antibiotic use have been being carried out in inpatient units since 2014. In 2018, the method was improved, the results of which established the way of further improvements. In the course of an ABS consultation we go through patients' relevant antibiotic treatments together with their physicians and discuss patients' further antibiotic therapies.
Methods: This is based on the following data: the antibiotic use on a given ward in the preceding 12 months, antibiotic resistance map and the rate of the emergence of multiresistant pathogens. During our work, we draw our colleagues' attention to the im-

portance of that sampling should always be performed properly and timely. By our contribution, we are aiming to increase the numbers of successful empirical and targeted antibiotic therapies.
Results: First part of our work started at the diabetology department. We are studying the antimicrobial therapy of the patients for three months along.The evaluation has been done in the month of January. In total of 17 patients received antibiotic therapy. 14 patients left the ward, 3 died, but not due to bacterial infection. Examining the therapy of 14 cured patients, we can say that 5 therapies were adequate and 8 were defective. There were two errors in the 8 failed therapy. Incorrect dosing was observed in 3 patients. No dose adjustment was made for renal function. Bacterial infection could not be confirmed in 5 patients. Probably due to inappropriate sampling. We would like to evaluate our February and March results in the same way. Then compare it to the typical antibiotic use in the first half of 2019.
Conclusion: On the base of the numeric data, we summarise our work and find out whether we managed to put our plans into action, and whether it is necessary to alter the methods of our consultations.

Investigation of gastric juice resistance of probiotic microcapsules in different formulations

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Background: Generally, probiotics are used in treatment for a variety of gastrointestinal disorders, however, their beneficial properties are not only useful in the sick organisms. They help digestion even in healthy gastrointestinal tract; reduce overproduction of gas producing and bile salt deconjugating species, thereby improving the digestion of food. They also increase the amount of nutrients that can be utilized, which is true for both the human and the animal body.
Aims: Our collaborative work is the microencapsulation of bacterial species used as probiotics for veterinary purposes: Lactobacillus plantarum, Bifidobacterium bifidum. The purpose of microencapsulation of bacterial species is to increase their survival at higher temperatures during feed pelleting and protect against the inactivating effect of gastric acid.
Methods: The probiotic strains were suspended in alginate solution and microencapsulated using a Büchi Encapsulator B-395 apparatus, than the microcapsules were precipitated in calcium chloride solution. In order to increase survival, biofilms of both bacterial species were formed by keeping the wet microcapsules of each bacterium for one day at room temperature. Groups of microcapsules were chitosan coated and lyophilized for further stabilization. Subsequently, dissolution testing was performed in artificial gastric juice. The microcapsules containing the bacteria were dissolved in peptone water, inoculated into the appropriate medium. After culturing, the effect of the treatments on viability (log N/N0) and the survival rate after acidic lysis was determined on the basis of CFU values.
Results: According to our results, the chitosan coating provided better protection against the acidic effect for bacteries. Among the probiotic strains, Lactobacillus plantarum showed higher survival compared to Bifidobacterium bifidum according to the pH optimum.
Conclusion: The probiotic strains were successfully microencapsulated, but the different formulations provided different degrees of protection against the acidic environment.

Prospect of image analysis in the evaluation of propellant-free foam characteristics

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Background: For decades the use of pharmaceutical foams was limited to dermal drug delivery. Not only are they proven to be sufficient drug carrier systems but the excellent patient compliance also makes them outstanding. Although the use of foams is becoming increasingly favored, the evaluation methods of this dosage form are yet far from extensive. Several properties, like stability or spreadability are related to the structure of the foam, therefor its investigation is largely informative.
Aims: This research aims to show the various ways image analysis can be used in the evaluation process of foams. Apart from the macroscopic attributes, like the height of foam and microscopic parameters, as the number, size and shape of the foam cells (bubbles) are similarly describable along with the size distribution of foams. The information allows assumptions on important foam characteristics, like bubble and foam-forming ability and stability.
Methods: Various propellant-free foam formulations were investigated in this study. Foams were produced in propellant-free pump devices from simple and complex surfactant solutions with and without active ingredient, as well as essential oil-containing microemulsions. Photos and videos were processed and analysed with image analysis software (ImageJ; Wayne Rasband, National Institute of Health, USA).

For stability assessment, dynamic light scattering and laser diffraction (Mastersizer 2000TM with Hydro SM instrument. Zetasizer Nano ZS; Malvern Instruments Ltd., UK) measurements were also carried out. Additionally, a test was carried out to examine the bubble forming ability of the initial liquids.
Results: The difference in the shape and size of bubbles in foams is clearly visible from the microscopic images. This deviation is also apparent at the characteristics of the foams. Further connection was found between the single bubble forming ability and the foaming.
Conclusion: Image analysis is an entirely applicable method for the investigation of macroscopic and microscopic foam characteristics consequently for the evaluation of pharmaceutical foams.

International illegitimate online pharmacy networks manipulate and dominate search engine Results:

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Background: The internet pharmacy market is dominated by illegal vendors selling unauthorized and counterfeit medicines. These products pose significant patient safety issues globally. Illegitimate pharmacy networks utilize abusive/underground marketing techniques including e-mail spam, forum abuse and search engine manipulation to attract customers. Although search engines typically refer consumers to relevant online resources quickly, search-redirection attacks refer consumers and patients from hacked websites appearing among top search results, to illegal online pharmacies operated by illegitimate actors.
Aims: We aimed to measure the prevalence of search-redirection attacks (hacking) among popular search engine results (SER) appearing in Google.hu for erectile dysfunction medications. Furthermore, to map and document redirection chain elements, and propose a methodology for closing down manipulated web links in collaboration with the national drug authority.
Methods: The four major active pharmaceutical ingredients: sildenafil, tadalafil, vardenafil and avanafil were searched on the most popular search engine Google.hu in August and October 2019. First 20 search engine query results were documented and evaluated manually, including SER ranking, link, redirect in source code, final destination website, and website relevancy.
Results: A total number of 111 links were evaluated during our two-month study period. The majority (n=72, 64.8%) offered erectile dysfunction medications for sale, while links promoting dietary-supplement accounted for 9.9% of SER, the rest being benign, irrelevant or not working. In August out of 55 relevant links 47 links were hacked and delivered visitors to 5 final international online pharmacies, while in October out of 46 links 35 were hacked, promoting 8 final destination pharmacy websites. These final destinations were all international illegitimate pharmacies operating in English.
Conclusion: Majority of the search results are illicit and within them compromised websites are dominant. The number and the SER position of websites affected by search-redirection attacks dynamically evolve over time, hacked links significantly outnumbering traditional unlicensed pharmacies. Shutting down such links in collaboration with authorities will likely clean up SER pages and prevent patients from accessing potentially dangerous pharmaceuticals.

Development of a complex visualization and quality management tool for the pharmacy curriculum

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Background: Current electronic administration systems do not collect and summarize prerequisites of obligatory subjects, data on student dropout rate, and integrate all relevant information in a visual map.
Aims: Development of a decision support and quality management tool supporting Faculty management and subject directors to further develop curriculum and optimize prerequisite subject structure.
Methods: Commercially available tools were tested, prerequisites of obligatory subjects were exported to various software aiming to visualize the networks. Dropout rates were collected from the electronic administration system (Neptun). A Windows Forms application was developed using C#.net.
Results: A curricular system can be considered as a graph containing nodes (subjects) and edges (prerequisites). The 10 semester curriculum is highly complex, as nearly 70 obligatory subjects have more than 110 prerequisites. Visualization in MS Project as a Gantt chart makes visual interpretation difficult. Network analysis and visualization software (eg.: Gephi), was also an inadequate tool to visualize the

timeline of education. A tailor-made software has been programmed integrating key subject specific components (credit value, subject code, semester, module, prerequisites, etc.) and educational properties (e.g.: failure rate, students' feedback on education), and a graphical user interface was developed for course visualization.
Conclusion: A network analysis and visual presentation of subjects require an individual software developed to meet our expectations and needs. Novel information technology methods will likely improve curriculum structure and reduce dropout rate by identifying critical subjects and affected students (e.g. by artificial intelligence).

New approaches to discover and evaluate pharmacy networks on the Internet

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Background: Due to the uncontrolled nature of the internet large number of illegal online pharmacies exist globally, violating international laws and distributing falsified medications. International and national authorities lack efficient tools to discover and close rogue websites down. Manual mapping and evaluating internet pharmacy website networks is incomplete, and wasteful for human resources. Thus, advanced computational methods are needed to detect and mitigate cybercriminal activity.
Aims: We aimed to develop a specific web crawler to better detect and classify illicit online pharmacies through text mining, content and link structure analysis.
Methods: The currently developed computer tool starts from a set of initial web sites determined from Google, where illegal pharmacies selling erectile dysfunction medications were searched for. The crawler downloads the web sites, determines it's and in the newt step downloads them. Again from these level 2 web pages the links are determined, and the process can be repeated infinitely. To avoid this exponential explosion of the number of web pages, conditions determine whether the page is relevant and whether the web page will be processed. The three basic conditions for relevance were: text of the web page must be in Hungarian, the domain of the web page should not be in a banned list, and four of eight keywords must occur on the web page at least once. The banned list of domains contained general 43 social web sites. The eight keywords were related to erectile dysfunction (tadalafil, cialis, vardenafil, levitra, sildenafil, viagra, avanafil, spedra).
Results: The 7 starting points were selected manually from the top 20 relevant search results from Google.hu in July 2019. A nine-level network of relevant web pages has been discovered, scanning lasted for approx. 150 minutes. The tool visited 6972 pages belonging to 289 domains, including 35 redirection pages, 488 duplicates, 199 non-Hungarian, 56 pages belonged to banned domains, while 1567 not contain the eight keywords. A total of 4253 pages were relevant, belonging to 94 websites found to be illegally selling erectile dysfunction drugs.
Conclusion: Due to the changing environment of search engines, and the changing behavior of illegal sites such novel computer tools are required. Further enhancement of the algorithms determining relevancy of the web pages, and an automatic classification tool estimating web site legality will increase sensitivity and specificity for the crawler.

Evaluation of the Hungarian pharmacy curriculum: results of a comprehensive national survey among pharmacists

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Background: There is an on-going change and progression in societal and professional expectations towards pharmacist, simultaneously role of pharmacists in healthcare are increasingly. Accordingly, modification of the 'Training and qualification requirements' has become an issue of the decade. Numerous professional bodies have identified areas for improvement.
Aims: We aimed to collect the opinions of practicing pharmacists (especially those who graduated in the near past) about Hungarian pharmacy education. Furthermore, to explore which areas and modules need to be changed based on their practical experience.
Methods: A 19 items online questionnaire was promoted nation-wide on professional forums and social media in November 2019. Questions were constructed, based on a previous survey of Hungarian Society for Pharmaceutical Sciences Youth Committee in 2014 as well as publications and suggestions from professional organizations. Graduates from the four universities were recruited to comment on the items and participate in the pilot of the questionnaire. We differentiate the respondents by the year and place of graduation, and area of practice. The

questions focused on the different modules and knowledge requirements needed to obtain a master's degree, as well as educational techniques and other training related topics.
Results: Numerous responses arrived (n=222) by the endo of November 2019, with 117 of those who have graduated between 2014 and 2019, representative for all areas of practice and universities. Majority of the responders answered that basic module's weight in education should be at least slightly reduced, and profession specific knowledge weight should be increased. The weight of education of pharmaceutical care, pharmacological and therapeutic knowledge must be increased according to the respondents, which is in accordance with the changed requirements towards pharmacists. Regrading the relationship of training to daily practice, most of the responders indicated that the training does not equip them with problem-solving skill, and the final exam does not assess the real employment demands.
Conclusion: Education in those topics which helps to prepare for patient and therapy-focused pharmaceutical service are much more needed in pharmacist training. Also, the answers provide guidance on which items in the curriculum may need focused attention.

Integration of pharmacist communication in English programs offered by European universities

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Background: The roles and responsibilities of 21st century pharmacists are evolving with their active participation in medication therapy management and pharmaceutical care in community, or medication reconciliation and antibiotic stewardship in hospital settings. These new professional competencies can improve therapeutic effectiveness, reduce risks of medication misuse and facilitate the rational use of financial resources. However, the need for advanced communication skills and strategies is essential.
Aims: We aimed to map trends in the education of communication skills and identify academic courses taught in English in European faculties of pharmacy in order to search for shifts towards a more patient centered and practice oriented pharmacist education.
Methods: The study included 14 universities of 11 different EU member countries, where pharmacy education was offered in English in 2019. Data on curricular information (e.g. title, course description, obligatory or optional course, number of lectures per semester, credit value) were selected and collected from institutional web sites.
Results: Pharmacist communication is an individual obligatory course only in 2 (in Debrecen and Prague) universities evaluated in our study. Another two institutions electively offer individual courses of communication and counseling (Szeged and Brno). Communication is integrated into Pharmaceutical Care in 3 universities, while into other obligatory courses in 3 other cases. In one institution academic English communication courses run for several years without integrating specialist language. In Denmark, training modules are used, in which communication skills are evaluated and integrated into pharmacy project assignments. Based on course descriptions and syllabus available from the university websites, communication skills are not an integral element of pharmacy education in 6 (42.8%) institutions.
Conclusion: Data reflect that the education of communication skills for pharmacy students show significant differences, while only a minority of faculties of pharmacy with English educational program in the EU integrate communication as an essential segment of pharmacist training today; nevertheless, its significance has been more widely recognized.

Antioxidant and antimicrobial activity of lyophilized flower extract of *Rosa damascena* L.

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Rosa damascena L. with origin in the Middle East, has medicinal functions that are partly attributed to their abundance of active compounds as flavonoids, glycosides, anthocyanins, terpenes. The constituents of this plant are responsible for antioxidant, anti-inflammatory, hypnotic, analgesic, anticonvulsant effect.
The aim of this study was to investigate the bioactive compounds, antioxidant capacity and antimicrobial activity of the extract. Using HPLC method was investigated the composition of phenolic compounds and the identification was achieved by comparison with retention times of standards. Determination of antioxidant activity of samples was made by DPPH, FRAP, CUPRAC and ABTS methods. The antimicrobial activity of the extract was determined by the disk diffusimetry method.
The result of total phenolic compounds using Folin-Ciocalteu assay was 321 mg GAE/100 g DW. The total flavonoid content determined by the colorimetric method AlCl3 was 32.4 mg QE/100 g DW.
Regarding the antimicrobial activity, the most sensitive antimicrobial effect was on the reference and the

clinical isolate of Pseudomonas aeruginosa strain. The high total polyphenols, flavonoids and anthocyanins content revealed that lyophilized rose petals represent a promising source of phenolic compounds which might be used as functional food ingredients and might be implicated in different antioxidant activity and therapeutic applications of this plant.

Brain activation pattern changes after acute citalopram administration during pharmacological magnetic resonance imaging (phMRI)

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Background: Citalopram, a selective serotonin reuptake inhibitor (SSRI) is widely used to treat several mental disorders such as depression. It takes 2-3 weeks to reach the full effect, but an acute citalopram administration increases synaptic serotonin content immediately and has a modulatory effect on information processing.
Aims: The aim of this study was to investigate alterations in brain activations pattern which can bring us closer to understand why altered serotonergic neural transmission leads to different neuropsychiatric disorders.
Methods: 32 (19 women and 13 men) healthy volunteers participated in two separate 30-minute scanning sessions, where they received normal saline or 7.5mg citalopram infusion in a randomized, double-blind trial. Data analyses was carried out in SPM12 software using flexible factorial method.
Results: After 7.5mg of acute citalopram administration a significant increased activation was detected in several areas of major brain networks such as the default mode network (posterior cingulate cortex, precuneus, MTG) the visual network (fusiform gyrus, lingual gyrus) and the sensorimotor network (postcentral gyrus). These activated brain regions show similarities with areas activated during an increased arousal.
Conclusion: The citalopram-induced increased synaptic serotonin content generate an arousal-like brain state. These neural changes can play a role in the acute side effects of citalopram and, in addition, induce downstream neuroplastic changes. Further investigations are needed to determine the exact therapeutic effects of increased synaptic serotonin among patients.

Acknowledgement: This study was supported by the Hungarian Brain Research Program (MTA-SE-NAP B and SE-NAP 2 Genetic Brain Imaging Migraine Research Group, KTIA_NAP_13-2- 2015-0001, 2017-1.2.1-NKP-2017-00002) and by the Hungarian Academy of Sciences (MTA-SE Neuropsychopharmacology and Neurochemistry Research Group), ÚNKP-18-2-I-SE-86 (G.K.) ÚNKP-18-3-III-ELTE-495 (K.N.), ITM/NKFIH TKP-SE; EMMI FIKP (SE- Neurology).

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Optimization of capillary electrophoresis conditions for the separation of gangliosides

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Background: Gangliosides are glycolipids that are present in microdomains in the outer leaflet of cell membranes where they are involved in the regulation of membrane-associated signaling proteins. According to recent studies, altered concentration of gangliosides has a potential role in the development of insulin resistance by modulating insulin receptor signal transduction. Gangliosides are structurally heterogeneous molecules composed of a ceramide portion and an oligosaccharide chain containing at least one sialic acid. They form micelles in aqueous solution, which hinders their separation as monomers by capillary electrophoresis (CE). Disruption of the micelles by cyclodextrins (CDs) was reported in previous studies using CE.
Aims: We aimed at optimizing a CE method for the separation of the most abundant gangliosides in biological samples.
Methods: Separation conditions including pH, buffer concentration and CD type and concentration have been optimized for the separation of gangliosides GM3, GM1, GD1a, GD1b and GT1b. The applicability of the method was demonstrated on biological samples.
Results: RAMEA (randomly methylated beta-cyclodextrin) as buffer additive was found appropriate for the separation of all five studied gangliosides. The best resolution was achieved at 15mM RAMEA in 100 mM sodium borate buffer. Mono-sialylated gangliosides GM3 and GM1 were separated in their native form for the first time by our CE method. Increased concentration of sodium borate buffer resulted in higher resolution due to the increased borate-carbohydrate complexation which results in additional negative charges on the analyte molecule. Increased resolution using more alkaline pH (10.0) where the complexation is most effective was observed, as well. The optimized method was applied on various biological samples, including ganglioside

extracts of rat brain, in which brain-specific gangliosides were identified, namely GM1, GD1a, GD1b and GT1b.
Conclusion: Separation of the studied gangliosides was achieved using the optimized method with RAMEA as buffer additive. This method was found appropriate for the analysis of ganglioside extracts from animal brain samples.

Advantages and disadvantages of the patient-oriented picking systems; How many is the wastage of packaging material?

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Background: More and more patient-oriented picking systems are used in hospital pharmacies to support the direct patients care of pharmacists. Undoubted advantage of these automated systems the increased drug & patients" safety, but at the same time have to take into consideration the question of pickings.
Aims: To measure the quantity of the unwanted packaging material produced in the course of operation of HD Medi automated patient-oriented picking system what is used in the Semmelweis University Pharmacy Korányi Department since 2018.
Methods: For 14 days all unwanted packaging material – the blisters and paper boxes produced at upset of cassettes, and the empty folia produced by automata during packaging, furthermore the traditional containers were collected on daily basis.
Results: During observational period content of 472 boxes were upset into the cassettes; it represented 1083 blisters plus 85 plastic container plus, 5299 ampullas were distributed from 956 boxes. The automate put in 10 907 bags but 22% of them were blank, that means waste as well. The whole quantity of wastage was 1103 litres, 22.6% of this was the blisters, and 77.4% paper wastage.
Conclusion: Problems we are facing at the moment – a lot of false error messages – time consuming – technical limits of identification and our assessment demonstrated that near 20% blank bags are produced by the automate.
The hope for technical assistance of the vendor could improve this mistake and by this way the wastage could be decreased. It would be a great help for the pharmacy workers if the drug companies provided in loose packages of the frequently used preparation for the hospitals. Further, in the interest of environment launching of the biodegradable drug packaging material would be appreciated.

Traditional uses of medicinal plants in the Southern Plain Region of Hungary

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Background: Traditional medicine is an important part of human health care. The uses of medicinal plants contribute a remarkable part of health care in many developing countries and also in developed countries, increasing their commercial value [1].
Aims: The aim of the present study was the estimation of traditional utilization of plants as medicine in the Southern Great Plain Region of Hungary. Field survey was carried out among the people who live in the affected area, and the ethnobotanical literature survey of the region was evaluated.
Methods: An interview line was created to assess the traditional knowledge of local communities concerning traditional plant utilizations in the affected area. A slideshow of plant photos was prepared and shown to every interviewer to elicit the plant species related knowledge. 25 field interviews were performed using the questionnaire. Population participating in the survey lives in Bács-Kiskun, and Csongrád counties. The ethnobotanical literature survey of the traditionally used plants and the scientifically proven activities and uses of them in medicine today are also collected.
Results: Data on local plant utilizations were processed and summarized, and literature survey was also evaluated. These data were reviewed with special emphasis on confirmed medicinal use, allowing the comparison of local traditional plant use with the scientifically proven data. Documentation of mode of production of several preparations made from plants was involved in the survey. Mainly the gastrointestinal, the respiratory system and skin problems were mentioned as therapeutic indication for which traditional herbal treatment can be applied. 60 plant species are outstanding in the research and the majority of the traditional plant uses are consistent with the scientifically proved uses, however, some specific plant utilisations were also recognised. The safety concerns of the plants were also considered in evaluation the data.
Conclusion: The informants usually proved to have broad knowledge about the plant use. This allowed gathering information about the cultural heritage and traditional uses of the local flora. The traditionally used plants considering the scientifically proven

activities and uses of them in medicine today provides a detailed, practical and research based approach to the use of modern herbal treatments.

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Possible mechanisms of drug-drug interactions in the medication of kidney transplant patients

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Background: In Hungary there are a growing number of renal transplant patients. Due to their immunosuppressive therapy and health status, they considered a high risk patient population. Moreover, these patients have various comorbidities, that lead to polypharmacy, which can potentially cause serious drug-drug interactions.
Aims: The aim of the survey was to assess the drug-drug interactions among our kidney transplant patients and to evaluate their clinical significance.
Methods: Within 24 hours of a patient's admission, as the part of the comprehensive drug history, a drug-drug interaction review was performed using Lexicomp® Drug Interactions tool. The interactions were rated by Lexicomp®'s rating system: X – avoid combination, D – consider therapy modification, C – monitor therapy, B – No action needed, A – no known interaction. Group B and A were excluded from the study to focus on the more clinically relevant interactions.
Results: During the pilot study (from 22/Oct/2019 to 25/Nov/2019.) there were 37 patients (51% male, mean age: 51) involved. The average number of concomittantly used medication were 11.78±4.81 per patient. 364 interactions were identified (X: 13, D: 35, C: 316) and classified. 3 problemes were highlighted: 1) The impaired absoprtion of mycophenolate mofetil due to administration of proton pump inhibitor 2) Polyethylene glycol as solvent of Bactrim infusion and metronidazole interaction resulting lactic acidosis 3) The potential vitamin D toxicity as a result of concomittantantly used active and inactive form of vitamin D.
Conclusion: Pharmacists should frequently monitor the immunosuppressant medication therapies, because of the latent absorption deviations. various adverse effects and potential drug-drug interactions. By the contribution of the clinical pharmacist in the medical team, the medication treatment could be more personalized and potential drug related interactions and adverse events could be decreased.

Antiproliferative cyclic C5-curcuminoids without DNA binding: design, synthesis, lipophilicity and biological activity in a SAR analysis

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Background: The chemical susceptibility of the ß-diketone linker between the two aromatic rings in the structure of curcumin to hydrolysis and metabolism has made it crucial to investigate structurally modified analogs of curcumin without such shortcomings.
Aim: The synthesis of twenty cyclic C5-curcuminoids is described in this study in order to gain more insight into their anticancer structure activity relationship (SAR). The design of their synthesis included four different cyclanones and five substituted aromatic aldehydes to form four, five-membered subgroups.
Methods: These model-compounds were evaluated in vitro for antiproliferative activity in an XTT cell viability assay against MCF-7 human non-invasive breast adenocarcinoma cancer cells and Jurkat human T lymphocyte leukaemia cells in five different concentrations (10nM, 100nM, 1μM, 10μM and 20μM).
Results: The majority of the compounds investigated have shown remarkable cytotoxicity with IC50 values in the range of 120nM and 2μM with very high relative toxicity values to curcumin. The SAR conclusions are drawn and summarized. A method was developed and applied in a TLC based experimental logP measurement, which is new for such C5-curcuminoids. The logP data and structural modifications have shown a strong correlation. The correlation of these experimental logP and the corresponding IC50 values of the model-compounds were calculated according to the Pearson and Kendall correlation coefficient and showed weak concordance. The physicochemical behaviors of the majority of these compounds are in good accordance with the Lipinski rules. The most promising compound is 7a, which is the most active (IC50=0.12-0.32μM), most potent (80 times of curcumin) with the lowest lipophilicity (experimental logP=3.22) which is important also from a pharmacokinetic point of view.
Conclusions: The analysis of experimental logP and computed ClogP values have revealed good agreement. These cyclic C5-curcuminoids, in contrast to

curcumin, do not bind to natural DNA based on their CD spectra.

Support: This study was supported by the European Union, co-financed by the European Social Fund (EFOP-3.6.1.-16-2016-00004).

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Formulation and investigation of creams containing Spirulina powder

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Background: Products containing natural active substances have an increasing role in therapy. Dietary supplements made using Spirulina algae have been in circulation for some time, but their external application is not so widespread, although Spirulina contains valuable ingredients with antioxidant and antibacterial effect.

Aims: The aim of our experimental work was to formulate creams containing Spirulina powder as a natural active substance. Creams containing penetration enhancing excipients were formulated. Various types of nonionic amphiphilic surfactants were used (Polysorbate 60, Cremophor RH 40, sugar-ester SP 50, SP 70). To enchance the penetration of Spirulina, through the skin, Transcutol was also added to our ointments as a solubilizer excipient.

Methods: The release of drug from the vehicle and its penetration through the membrane were determined by Franz diffusion cell. The cytotoxic effect of compositions was evaluated by a colorimetric method (MTT) on HaCaT keratinocyte cell line. The antioxidant effect of Spirulina-containing creams was also investigated on HaCaT cells. The cells were exposed to UV-B radiation, pre-and post-treated with samples containing Spirulina powder in different compositions, and superoxide dismutase (SOD) activity was measured. The antimicrobial activity of Spirulina cream was checked against Propionibacterium acnes with turbidimetric method.

Results: Cream containing sugar-ester SP 70 as emulsifying agent was the most preferred composition according to the diffusion and MTT tests. The penetration rate was the highest from this formulation. With the addition of Transcutol higher release of Spirulina was observed. The diffused amount of active substance thus reaches 40% in the case of a cream containing SP 70 emulsifying agent. Thanks to the Spirulina treatment the activity of antioxidant enzyme was increased in the cells. In those compositions where Transcutol was added to dissolve the Spirulina powder we detected higher increase in the SOD activity. According to the result of antimicrobial test Spirulina cream could be effective against *P. acnes*.

Conclusion: In conclusion, o/w creams with appropriate consistency were formulated. Transcutol with sugar-ester type emulgents elevated the amount of active substance across the diffusion membrane. Sufficient antioxidant activity was measured against UV-induced oxidative stress on HaCaT cells. Spirulina cream showed antimicrobial effect against *P. acnes*, so it can play an important role in the treatment of acne vulgaris.

Formulation development of Telmisartan driven by flux measurements

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Background: Utility of in vitro flux measurements in formulation development and bioequivalence prediction have been explored in a number of recent studies. The benefits of such measurements are based on the fact that they capture the complex interplay between effects of formulation ingredients on solubility, dissolution rate and permeability of an active pharmaceutical ingredient (API).

Aims: The aim of this project is to prove the applicability of instruments and methods as biorelevant tools incorporated in drug formulation development.

Methods: PAMPA Measurements Each well of the top compartment of 96-well STIRWELL PAMPA sandwich was coated with n-dodecane. Before forming the sandwich, the bottom and top plate was prefilled with suitable compounds. After 30 minutes the PAMPA sandwich was separated and 100 µL of both the donor and acceptor compartments were transferred to UV plates. UV absorption was measured with Tecan Infinite M200. FLUX Measurements Electrospun formulations of TEL were tested using MicroFLUX and final forms of TEL were tested with MacroFLUX. Concentration in both chambers were monitored in real time using in situ fiber optic dip probes connected to the Rainbow instrument. An artificial membrane impregnated with n-dodecane to form a lipophilic barrier between the donor and acceptor chamber.

Results: The excipients of the available TEL formulations and widely used standard excipients were in-

volved in the first API-excipient investigations. The surfactants have significant reducing effect, while the polymers have a slight, non-significant increasing effect. Mixed effect were experienced with fillers, where mannitol provided a lower flux and permeability then the others. Due to the permeability decreasing effect of surfactants and increasing effect of polymers, amorphization has been selected as the formulation strategy, which we implemented by electrospinning. To simulate the in vivo conditions, media change was carried out after 30 minutes. During the first 30 minutes of the experiment no flux across the membrane was detected because of the charged state of the API, while after media change TEL started to permeate through the membrane. The developed formulations provided similar flux profile to Micardis.

Conclusion: The described formulation development procedure demonstrated how excipients can be classified in the early stage of excipient selection and the most advantageous ones can be used in the later stages to ensure suitable behavior of the final product.

Synthesis and characterization of novel cyclodextrin-based drug-carriers targeting the central nervous system

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Background: Blood-brain barrier (BBB) segregating the central nervous system (CNS) from the systemic circulation inhibits also the delivery of therapeutics into the brain. As glucose transporters are overexpressed on the surface of the BBB, they provide ideal targets for new drug carrier systems aiming the CNS [1]. Another approach is the use of positively charged carriers to achieve high affinity for the negatively charged endothelial cells of the brain capillaries. It is also evidenced, that organizing monomeric compound to macromolecular systems enhances their transport across the phospholipid membranes [2].

Aims: As cyclodextrins (CDs) are known as ideal drug carriers, our aim was to develop new CD-based drug delivery systems, capable to cross the BBB.

Methods: Based on the aforementioned considerations, we have synthetized two sets of CD derivatives: (1) glucose appended beta-CD (BCD) and hydroxypropyl-BCD (HPBCD) scaffolds using click-chemistry, (2) positively charged polymer by crosslinking (2-hydroxy-3-N,N,N-trimethylamino) propyl-BCD (QA-BCD) with epichlorohydrin.

Results: For the in vitro investigation of the compounds, their fluorescent labeling was necessary. As fluorescent tags, 7-alkylamino-4-nitrobenzofurazan (NBF) and fluorescein-isothiocyanate (FITC) were used. The labelled glucose-modified CDs were synthetized by the simultaneous attachment of the fluorophore and a targeting unit via click-reaction and characterized by NMR and MALDI-TOF-MS. The FITC-labelled polymers were synthetized through a copolymerization of the QA-BCD and 1% FITC-BCD monomer and characterized using NMR and dynamic and static light scattering. The cellular internalization properties of the conjugates will be investigated using isolated human brain microvascular endothelial cells (HBEC-5i). The HBEC-5i monolayer serves as a barrier model. Confocal fluorescence microscopy is used to determine the internalization process and flow-cytometry is used to quantify the cell-penetration. In vitro properties of the conjugates are under investigation.

Conclusion: Various new CD-based drug carriers targeting the CNS have been synthetized and characterized by NMR, MS and microscopy.

The authors kindly appreciate the financial support for Gedeon Richter Ltd and for the ÚNKP-19-4-SE-53 fellowship (S.B.).

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Study of interaction of reduced glutathione (GSH) with some chalcone analogs in vitro and in vivo

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Background: Chalcones are intermediary precursors of flavonoid biosynthesis. Both natural and synthetic chalcone analogs are proven to have various biological activities. In our previous experiments, some cyclic chalcone analogs showed a significant effect on GSH status of Jurkat T lymphocyte cells, and most of the investigated chalcones displayed spontaneous GSH-reactivity.

Aims: The aim is to demonstrate A) the relationship between GSH-reactivity of chalcones and their anti-cancer properties; and the influence of this reactivity on their other biological effects. B) How the ring size, substituents, and pH affect the reactivity and stereochemistry of the reaction. C) to compare luminal elimination kinetics and metabolism of our chalcones and their bis-Mannich-base analogs.

Methods: For analyzing the in vitro incubates, proper RP-HPLC-UV-VIS and HPLC-MS methods were

developed. In the case of the in vivo experiment, the isotonic buffer of the two compounds was perfused for 90 minutes in anesthetized rats, and monitored using a validated method of HPLC-DAD as well as HPLC MS.

Results: Most of the compounds showed an intrinsic reactivity towards GSH. This reversible reaction yields two diastereomeric adducts in case of open-chain chalcones (in both in vitro and in vivo), and four ones in the case of cyclic chalcones. The open chain and six-membered chalcone derivatives showed the highest reactivity. The methyl and dimethylamino derivatives displayed the highest and lowest GSH reactivities respectively. Mannich analogs showed more reactivity than their parent compound. In the in vivo experiment, Mannich analogs showed a lower rate of absorption and a higher rate of elimination in comparison to chalcones. In the small intestine perfusates, the chalcone and Mannich analog, and their glucuronide, sulfate and glutathione-conjugates were detected.

Conclusion: The rate and mechanism of the reaction is found to depend on the ratio of deprotonated to protonated GSH. Reactivity of the chalcone derivatives was also found to depend on the aromatic substituent of the A ring. Based on the results, the GSH reactivity does not seem to be a direct determining factor in the cytotoxic effect of the compounds. Our in vivo experiments demonstrated that the GSH-conjugation reaction of chalcones plays a role in the fate of the per os administered compounds.

This study is supported by the European Union, co-financed by the European Social Fund (EFOP-3.6.1.-16-2016-00004).

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Logistic and storage management of cytotsatic infusions

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With the increased occurrence of malignancies in the past decades the demand for cytostatic infusions increasing rapidly. Their centralized production and distribution are a big challenge for hospital pharmacies worldwide.

The preparation of cytostatic infusions by computer aided gravimetric methods (CATO) was introduced in 2017 for Department of Oncology. Since the beginning of 2020 Department of Pulmonology and Gynecology have joined the CATO system.

The protection of the professional staff, the patients and the environment is ensured by the temperature control transport of cytotoxic infusions and the regulations of international guidelines (ESOP).

The cytostatic drugs are stored in separate storeroom equipped with „spill kit" which is available in the transport van also. In addition the containers are marked with international „yellow hand" symbol. The staff is being trained regularly how to manage an accidental contamination.

Cytostatic infusions are delivered by thermo controlled vehicles. The transport packaging guarantees that breakage and contamination cannot occur. The containers are equipped with international symbol, which consist of "yellow hand" pictogram and a short warning message.

Collaborated care, specific instructions and precautions are needed in the handling and transport of chemotherapeutic drugs. In addition to the design of therapies and the preparation of infusions, the logistics, patient safety, protection of employees' health and environment is key task.

Development of oral peptide drug delivery systems

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Background: Therapeutic proteins have become the treatment of several diseases due to their bioactivity and specificity. At this point, injections mean the most common way for administering proteins and peptides because of their extremely low oral bioavailability. Efforts to improve bioavailability of orally delivered proteins have been intensified over the years and several approaches have been recommended like the chemical modification of the protein, or the formulation of carrier systems.

Aims: The object of our research was to formulate innovative sodium alginate nanospheres of a peptide type API by controlled gelification method. Thus, our aim was the calibration and settings optimization of the encapsulator instrument as well. We have been also evaluated the cytotoxicity of different penetration enhancer excipients.

Methods: Formulation has been performed by controlled polimerisation method with the help of Büchi Encapsulator B-395 Pro. For the formulation, we used 1.5% sodium alginate solution as encapsulating polymer, and 100mM calcium chloride dihydrate solution as hardening solution. In vitro dissolution has been evaluated to characterise drug release from the beads with an average diameter of 200μm. The drug concentration in each sample was analysed by radioimmunoassay. Biological properties of the excipients

had been evaluated as well with MTT assay on Caco-2 cells. To determine swelling behavior of beads, dry beads were weighed and placed in distilled water for an hour, then zhe equilibrium water uptake was determined. Particle size distribution of the beads with an average diameter of 200μm has been performed with laser diffraction technique in a collaboration with Budapest University of Technology and Economics.

Results: Over the last few months, we have successfully determined the optimal parameters and settings for the formulation using 200μm nozzle. According to the results, it can be concluded that the whole amount of the encapsulated API was detected after 60 minutes. The results of MTT assay showed that the selected excipients are safe under in vitro conditions. The physical analysis of the beads proved that real particle size is close to the theoretical water uptake depends on the size of the beads.

Conclusion: Our results suggest that these microbeads may provide a traditional oral pathway for the delivery of peptides.

Enhancing of primycin production by Saccharomonospora azurea with various fatty acids

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Background: Primycin, produced by a Gram-positive filamentous bacteria *Saccharomonospora azurea* is a 36-membered marginolactone antibiotic, which possesses high antimicrobial activity against several clinically important bacterial pathogens. Like other guanidino marginolactone antibiotics, primycin is biosynthesized through the bacterial modular type I polyketide synthase (PKS) multienzyme, which assembly mechanism is closely related to fatty acid (FA) biosynthesis. Since the biosynthesis of polyketides and FAs share common precursors via acetyl-, and malonyl-CoA, the two pathways may compete for substrate, which can affect the yield of antibiotic production.

Aims: The aim of present study was to determine the impact of various fatty acid substrates on primycin production, thereby find out the fatty acid substrate specificity of the primycin PKS pathway during antibiotic biosynthesis.

Methods: To evaluate their potential to enhance fermentation performance, the effect of stearic acid (C18:0), palmitic acid (C16:0), lauric acid (C12:0), capric acid (C10:0), enanthic acid (C7:0), caproic acid (C6:0), and butyric acid (C4:0) in growth medium were investigated. Among the tested fatty acids, those with highest primycin production inducing ability were selected and further investigated in a time course experiment. In order to determine primycin concentrations of fermentation medium, HPLC-DAD-MSD analysis was performed.

Results: The data demonstrated that stearic acid and palmitic acid possess the highest primycin production inducing ability among the examined fatty acids. Our results clearly show that palmitic acid was a better alternative of the originally applied stearic acid in all tested concentrations, while 4.5g/L proved to be the most effective.

Conclusion: The present study revealed that palmitic acid plays an essential role in primycin biosynthesis and may be used not only as an alternative component of stearic acid in the fermentation media but could serve as a standard component of a newly designed and highly effective primycin producing fermentation media.

Synthesis and analysis of opioid glycine-hapten derivatives

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Background: Drugs of abuse are small molecules that typically do not induce an antibody response following injection or inhalation. To induce antibodies against small molecules, structural surrogates of the molecules, which were named "haptens", must be coupled to immunogenic proteins, called "carriers". These structural surrogates are typically drug-linker adducts, in which the linker has a terminal functional group that forms a covalent bond with the carrier. The efficacy of these conjugate vaccines depends on several factors including hapten design, coupling strategy, hapten density, carrier protein selection, and vaccine adjuvant.

Aims: Synthesis and structural analysis of potent hapten-like morphine derivatives.

Methods: We designed N-substituted morphine compounds and for this purpose the normorphine-derivatives were required. Morphine, codeine, their dihydro derivatives, oxymorphone and oxycodone were N-demethylated with alfa-chloroethyl chloroformate. After receiving the appropriate hapten molecules the next step was the coupling phase with glycine ethyl ester. Unfortunately the reactions didn't work or the work-up process was not possible. As an alternative route the normorphine-compounds were reacted with N-chloroacetyl glycine ethyl ester. If purification was needed column chromatography

was used. The structures of the new compounds were determined by NMR and partially mass spectroscopy. These products were hydrolysed in alkaline media and after the work-up process all of the derivatives contained the free carboxylic group of the glycine sidechain, confirmed by NMR measurements. All of the glycine ester and the glycine carboxylic acid derivatives (except the norcodein ones) are under biological tests.

Results: Previously 12 hapten type molecules were synthetized from another 12 ethyl ester precursors. To model the peptide connection 6 glycine ethyl ester derivatives were obtained and all 6 have been hydrolysed to achieve the free acidic forms. 8 of the 12 N-acetyl-glycine-nor-compounds are under biological studies. The other molecules are under physico-chemical measurements. The structures of all of these molecules are confirmed by NMR spectroscopy.

Conclusion: We have developed different reaction ways to obtain 36 hapten-like normorphine derivatives and 32 of them are synthetized for the first time. The most potent compounds are under biological experiments. Right now we are working on new sidechains to change the linker and the amino acid part as well.

How can we improve patient collaboration?

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Background: The definition of adherence in the WHO's wording is "the behavior of an individual in accordance with recommendations of a health care professional in the field of medication, diet and lifestyle changes". Adherence is when an individual interacts with medication and / or lifestyle modification in accordance with health care recommendations during therapy. This also requires the same quality of information from a healthcare professional, wherever they are available.

Aims: The purpose of the presentation is to highlight two issues that hinder patient collaboration: 1. packaging problems: confusing packaging, changing the usual packaging, empty blisters, hard-to-open containers, incorrectly sized measuring instruments, home-cooking problems. 2. Expedition of suspension formulations from special dosage forms: eg. steroid nasal sprays, steroid eye drops, inhalation suspensions, home-made antibiotic suspensions.

Methods: As a method, we conduct a questionnaire survey with more expeditioners and patients. By presenting individual examples and processing the questionnaire, we would like to draw attention to some problems in the freight forwarding practice. The questionnaire examines the accuracy of the information received and the effect of the "Shake Before Use" instruction for the above mentioned preparations. Another highlight is the problem of packaging. The so-called. since the introduction of the tepee-safe boxes, it has not been possible to check whether the grade prescribed by the prescribed medical instruction is in place. packaged next to an antibiotic suspension, but it is also problematic to dispense formulations that are almost identical in packaging but have different effects.

Results: After evaluating the questionnaires, we will be able to draw the final conclusion.

Conclusion: Finally, we would like to make a recommendation to resolve the issues we have discovered so that we can further improve the safe medication practices for patients.

Transcriptomic studies in animals – TRPV1 and TRPA1 as key players in migraine?

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Background: Transcriptomics are gaining relevance for gathering knowledge about diseases more precisely. Migraine is a complex disorder not fully understood and the pathophysiology is still not clear.

Aims: After reviewing transcriptomic studies in migraine the genes transient receptor potential cation channel subfamily V member 1 (TRPV1) and transient receptor potential cation channel, subfamily A, member 1 (TRPA1) emerged as possible contributors to migraine headache.

Methods: I have reviewed some of the latest articles and extracted the most relevant results.

Results: These two genes were differentially expressed in animal studies using a nitroglycerin-induced migraine model. With ADM_12, a TRPA1 antagonist, and ghrelin, a substance tested to influence TRPV1 expression, it was possible to counteract both expression changes. TRPA1 is situated in nociceptive neurons in which TRPV1 channels and neuropeptides such as CGRP or Substance P are expressed. It was also shown that TRPV1 receptor induction releases the neuropeptide CGRP that has neurovascular and proinflammatory effects. Furthermore, the TRP ion channel family could be found surrounding the trigeminal ganglia, trigeminal nuclei and their vessels, regions strongly associated with pain sensation.

Conclusion: These findings suggest that these two channels might be important contributors to migraine headache.

Investigation of solubility and enhancement of biological activity of chrysin

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Background: Chrysin is a bioflavonoid that can be found in nature which possesses several biological effects (anti-inflammatory, antioxidant). However, chrysin is poorly soluble in water and so its bioavailability is reduced.
Aims: The aim of this research is to investigate the chrysin solubilization capacity of different β-cylcodextrins derivatives and compare their biological activities to each other's.
Methods: 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 anti-inflammatory action was studied by immunofluorescence, labelling the p65 subunit the inhibition of NF-κB pathway activation. The antioxidant capacity of complexes was determined by SOD, GPx and ORAC assay.
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 100μM concentration the examined complexes were not cytotoxic on Caco-2 cells. Investigating the NF-κB inflammatory pathway we found that the 1:1 Chrysin-Cyclodextrin complexes decreased more efficiently the TNF-α-induced nuclear translocation of p65. SOD activity in the cytosol after treatment with complexes show the correlation with cell permeability test results in which both 1:1 and 1:2 ratio complexes show the efficacy to improve chrysin permeation. According to ORAC assay results, it is proved that with increasing molar ratio of complexes, the solubilized concentration of chrysin is increasing.
Conclusion: In conclusion, cyclodextrin derivatives can effectively improve the water solubility of chrysin and the formed complexes are not cytotoxic in the tested concentration range. The complexes can inhibit the NF-κB inflammatory pathway, and cyclodextrins had not activated the pathway. The in vitro ORAC antioxidant test and in vivo SOD and GPx assay showed different correlation with molar ratio of complexes.

The development of a semi-solid formulation containing natural extracts as a hand-sanitizer preparation

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Background: Hand sanitization is an important step in both everyday life and health care. However, it is a general experience that this process is not always correctly performed, moreover many users are reluctant to use preparations containing synthetic materials. According to the results of hand hygiene compliance measurements, in many cases, medical personnel use gloves instead of hand sanitizer.
Aims: Nowadays, the demand for natural, plant-based preparations is increasing. Our work aims to produce a semi-solid composition containing essential oils which in addition to its favorable technological properties and applicability, can be used effectively to sanitize the hand according to European Standards [1]. Some plant-based materials have been shown to have bactericidal activity without the development of bacterial resistance [2]. Thus, the use of such a product provides new possibilities for hand sanitization.
Methods: In the first phase of the work, we designed a gel capable of delivering the components responsible for antimicrobial activity at appropriate concentrations during use without leaving a sticky or tacky residue after absorption. After formulation, examination and physicochemical tests were conducted according to the Hungarian and European Pharmacopoeias including; rheometric, dissolution and diffusion tests, microscopic examination, extensometric test, pH measurements. Next, the evaluation of bactericidal activity was performed. The effect of the prepared gel on the resident bacterial flora of the hand skin and hygiene were monitored by swab sampling for microbiological testing.
Results: Our results show that the physicochemical stability of the formulation appears promising. Moreover, it has good technological properties and applicability and has been proven to be effective against the microorganisms tested (*Staphylococcus epidermidis, Staphylococcus aureus,* and *Candida albicans* among others).

Conclusions: Results suggest that the gel can be used as an adjuvant hand-sanitizer in basic health care. It is easy and fast to use, making it more convenient to sanitize the hand of the health care personnel, for example, between two patient examinations or drug administrations.

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Synthesis of amphiphilic sialic acid derivatives

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Background: Influenza is a widespread disease worldwide and its pathogene is one of the 10 deadliest viruses. In 2019, WHO drew attention to the dangerousness of influenza. It can be the greatest threat for the population of the World. Therefore, development of new medications with new mode of actions against influenza is necessary and inportant. [1]. Influenza has two glycoproteins on its surface: hemagglutinin (HA) and neuraminidase (NA). HA helps the attachment of the virus on the host cell's surface, it recognizes and bonds to the terminal sialic acid molecules of the receptors on the surface of the host cells. After replication NA hydrolyses the glycosilic bond of the sialic acid moieties and helps to release the newly formed viruses. The currently used NA inhibitor are not effective enough.
Aims: Unfortunately, there are no hemagglutinin inhibitor in use, although the usage of these types of drugs could solve the problem of resistance, because if the attachment of the virus on the host cell is inhibited, the infection and mutation can not be occurred. Therefore, we decided to prepare multivalent sialic acid derivatives to trap influenza through hemagglutinin.
Methods: We have synthesized lipophilic sialic acid derivatives. As carrier molecule methyl α-D-glucopyranoside was used, it was equipped with two lipophilic chains (butyls, octyls, and decyls). Into position 6 a tetraethylene glycol chain was introduced bearing azido group and a propargylated sialic acid derivative was conjugated to this azido group by a 1,3-dipolar cycloaddition reaction.
Results: The octyl derivative is proved to be active against *influenza A* and *B viruses*.
Conclusion: In water these molecules can form aggregates, these aggregations may mimic the surface of the host cell, and they may trap influenza viruses. In other way they could inhibit the attachment of the virus by the possible interaction with the lipid bilayer of the host cell or the virus.

Method development for the simultaneous HPLC testing and sterility determination of dorzolamide hydrochloride and timolol maleate containing eye drops preserved with benzalkonium chloride

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Background: After the risk based safety mapping of the internet market of eye drops, the dorzolamide hydrochloride and timolol maleate containing eye drops were selected as products with the highest patient- and medication safety risk. Three product samples (multi-dose eye drops, preserved with benzalkonium chloride) were purchased for quality control tests.
Aims: Our aim was to develop a method for the determination of the quality of online purchased multi-dose eye drops and quantify medication safety risks.
Methods: Due to the small amount of samples (5ml), we only designed assay with HPLC and test of sterility. Six HPLC methods described in the literature proved to be suitable for the co-examination of active substances and two for the determination of the microbiological preservative in these solutions. The method for determining the 3 components together was not found in the literature. The sterility testing was completed according to the European Pharmacopoeia.
Results: We first had to set up the HPLC method and test the eye drops. Subsequently, the total amount of samples were used for sterility testing. Sampling was performed in A grade, aseptic space because of later test of sterility. Liquid chromatography was performed on a WATERS STERISORB ODS1 C18 (5μm, 25cm x 4,6mm) column and the mobile phase consisted of an acetonitrile: phosphate buffer (pH 2.5): methanol (5:85:10 v/v/v) mix and a flow rate of 1.0ml/min and equipped with a Shimadzu SPD-20AV DUAL UV/VIS detector at two fixed wavelengths (210.0 nm and 250.0nm). The retention times for dorzolamide hydrochloride and timolol maleate were found to be 8.5 and 3.2min (250nm). The benzalkonium chloride gave two peaks at 11.5 and 23.4min. Membrane filtration technique was used for sterility testing. Validation of HPLC and microbiological assays was performed using original multi-dose formulations purchased from a community pharmacy in addition to the reference standards according to the ICH guideline. The HPLC and microbiological analysis are in progress.

Conclusion: The HPLC procedure was successfully applied to the simultaneous determination of these compounds in pharmaceutical preparations. Our results will demonstrate the medication safety risks of internet purchased ophthalmic medications and the potential public health concerns of illegal internet market of pharmaceuticals.

Non-genomic actions of steroid hormones on pregnant uterine contractions: an in vitro study

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Background: It has proven the prompt action of steroids is independent of their Genomic pathways, the correct mechanism of this fast-action which called as non-genomic pathway still needs to do more investigation.
Aims: Was investigate these actions of 5 types of steroid hormones on pregnant uterine contraction in rats.
Methods: Uterine tissues from 22-days-pregnant SPRD rats were dissected and mounted in an organ bath. Myometrial contractions elicited with KCl then cumulative dose-response of 17β-estradiol, progesterone, testosterone, fludrocortisone, and dexamethasone were recorded and statistically analyzed with unpaired t-test. In another set of experiments, the samples were pre-incubated with the following drugs before stimulation with KCl: (1) with cycloheximide, a protein synthesis inhibitor and actinomycin D, a transcriptional inhibitor for 30 minutes. (2) with the specific steroid hormone receptor antagonist of different types of steroids for 10 minutes; fulvestrant for 17β-estradiol, spironolactone for fludrocortisone and mifepristone for progesterone, and dexamethasone. (3) with mifepristone for all types of steroids. later, the endothelium of uterine tissues was removed by scratching, the experiment repeated to observe the effect of myometrium alone.
Results: Both 17β-estradiol and testosterone showed 60% while dexamethasone, fludrocortisone, and progesterone had 28, 24 and 40% relaxing effects, respectively. The remove of the endothelium or use of Actinomycin D and cycloheximide did not change the responses of any steroids. Specific antagonists did not block the effects of testosterone, fludrocortisone, and progesterone. Mifepristone (10^{-8}M) inhibited the effect of dexamethasone. Surprisingly, a high concentration of mifepristone (10^{-6}M) blocked the effects of all steroids, except progesterone.
Conclusion: In the 30min period of the experiment, we observe all types of steroids had a relaxing effect. the actions are not related to the genomic pathway and located on the pregnant myometrium. 17β-estradiol and testosterone have the strongest effect, while the actions of dexamethasone, progesterone, and fludrocortisone are moderate. Their actions (except dexamethasone) were resistant to their specific antagonists. Mifepristone seems to be a general blocker of non-genomic action of steroids (except progesterone). Non-genomic, prompt actions of steroid hormones inhibit pregnant uterine contractions, it might be a key for future investigation and be beneficial during preterm birth.

Lipid peroxidation and ibuprofen metabolism in hyperglycemic rats with *in-vitro* oxidative ibuprofen modifications

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Background: Hyperglycemia considered as a source of diabetic complications via induction of oxidative stress generating a higher rate of reactive oxygen species (ROSs). They have a significant role in the onset of both types of diabetes, and ROSs can oxidize non-enzymatic, endogenous and exogenous molecules. ROSs react with sensitive cellular macromolecules (nucleic acids, lipids, proteins) and exogenous (e.g. drug) molecules to form characteristic products. The latter is not well studied in the diabetic environment.
Aims: This study is an effort to better understanding of how oxidative stress develops diabetic complications in STZ-treated rats, and to what extent oxidative stress modifies the metabolism of ibuprofen (IBP), as an example of an exogenous compound. In addition, in vitro non-enzymatic oxidation of IBP modification was studied.
Methods: STZ-treated (hyperglycemic) rats were studied for four weeks. Then, the level of peroxidation was examined by means of a) UV-Vis determination of malondialdehyde (MDA), and b) HPLC-UV-Vis determination of lipid peroxidation (LP) generated carbonyl compounds. Glutathione (GSH) level was determined by UV-Vis method. For comparison, the oxidative metabolism of IBP was studied by analysis of the intestinal perfusate of the rats. In addition, in-vitro Fenton and Udenfriend tests were performed to evaluate non-enzyme-catalyzed oxidation of IBP. The structure of the investigated derivatives and products was proved by LC-hrMS.
Results: The MDA level was slightly increased in the 1st week of the liver and the small intestine and decreased in the 2nd and 4th week of the small intestine. GSH level of the small intestine and the liver was significantly elevated in all groups, but the 4th-week

initiates to become falling. While MDA and HNE (DNPH-derivatives) could not be identified. In general, chromatograms of the liver and the small intestine extracts were not significantly different from that of the control samples. In vitro, 1-OH-IBP, 2-OH-IBP and IBP-COOH were formed in the Fenton reactions and Udenfriend hydroxylation test.
Conclusion: Hyperglycemia can promote ROS accumulation through different metabolic pathways. The results of the 1st week (increased MDA) gives evidence of increased ROS production. Lack of increase in the secondary carbonyl LP products indicates that the oxidative and reductive enzymes effectively transform them in the liver and small intestine. The increased GSH levels can be the result of the increased ROS formation, which induces GSH biosynthesis.

Do newly initiated drug treatments pose real risk to chronic drug users? Prospective drug-drug interaction survey among hospitalized patients

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Background: Medical treatment is often initiated in patients admitted to the hospital. Adhere to the „nil-nocere" concept, assessment of drug-drug interactions and avoidance of iatrogenic harm is an important patient and drug safety issue. On the other hand, only minority of drug drug interactions are clinically relevant and some of them are beneficial. Clinical pharmacy services include assessment of drug-drug interactions upon initiation of new medicines.
Aims: Assessment and evaluation of drug-drug interactions between newly initiated drugs and between newly initiated and chronic drugs.
Methods: Thirty-thirty consecutive patients admitted to the orthopaedics and oncology units in 2019 August were included in the study. Medication use were retrieved from patient charts. Interactions between active agent were analysed by the Lexicomp® Drug Interactions module of the UpToDate database. Drug-drug interactions were classified into five categories (A, B, C, D, X) depending on the severity of the possible interaction.
Results: Data of 59 patients were analysed. Overall, study patients took 641 different drugs (on average 10.9 drugs/patient) of which 70% (451 drugs) were chronic drugs. Polypharmacy (use min. 5 drugs concomitantly) was present in 91.5% of patients. We detected 741 possible interactions which belonged to 57 patients. Most drug-drug interactions (389, 52.3%) occurred between chronically used medications. Only 14 interactions were rated as X-category (avoid combination) and affected 11 patients. Out of these 14 interactions, only one interaction affected a newly initiated drug treatment with modest reliability. In the other 13 cases, the two interacting chronic drugs were used parallel without any clinical problem.
Conclusion: Although possible drug-drug interactions affected almost every patient, but number of clinically relevant, possibly severe drug-drug interactions were limited and has not been clinically manifested. Interaction databases detects many irrelevant, insignificant interactions.

Measurement and evaluation of pre- and postoperative pain relief in surgery of herniated disc

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Background: Despite the availability of modern analgesic drugs, tools, techniques, the pain management is a major challenge. In the case of surgical interventions, a proper pain relief has an important role in particular the postoperative analgesia. Use of analgesic techniques not only improve the patient's well-being and general condition but also contribute healing by alleviating the body's inflammatory and mechanical reactions.
Aims: All neurosurgical interventions, especially for spinal surgeons, are characterized by the constant presence of increased pain in the preoperative period. Thus, analgesia is important both in the pre-operative and post-operative stages. Our aim was to review, evaluate and optimize the protocol for chronic pain therapy in case of the pre- and postoperative conditions.
Methods: During the 5 months of research, we could chance to approach to he patient interview and medication history. We have been informed about chronic pain and the used pain management techniques, furthermore, measure the pre- and postoperative pain on the day of surgery and for another two days using a visual analogue scale (VAS) and pain-related questions. We have studied the drugs taken by patients previously, the active pharmaceutical ingredients (API), the dose, the administration's time of premedication and analgesics used during the intraoperative and postoperative periods. In addition, we evaluated the effects of drugs taken during the postoperative period and contributed to the development of post-operative pain management techniques.
Results: The patient's pain perception is positively influenced by the appropriate therapy. Continuous,

empathic management of pain sensation improves patient adherence and compliance. Proper pain relief can reduce the days of hospitalization to three or two days. Furthermore, the use of intravenous analgesics could be reduced only for the day of surgery, then pills can be used. These lead to lower costs.

Conclusion: There is no general analgesic solution that can be used by all patients, it needs to be personalized. Initial surveys, clinical pharmaceutical intervention, and ongoing feedback are crucial in the development of individual therapies. This also means that the monitoring and method of questioning, the techniques used and protocols need to be continuously improved.

Analysis of HCTZ use and the skin cancer risk among the patients of Semmelweis University, Dermatological Department

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Background: A recommendation was issued by the EMA on 1st October 2018 to improve awareness about the increased risk of certain non-melanoma skin cancer (NMSC) types (basal cell carcinoma and squamous cell carcinoma) following higher cumulative doses of hydrochlorothiazide. Various epidemiological observations suggest a correlation between cumulative dose of hydrochlorothiazide (HCTZ) exposure and the increased risk of NMSC. Though results are ambiguous, they support a cumulative dose-dependent assotiation between HCTZ and NMSC.

Aims: This study aims to identify therapeutic HCTZ exposure in the anamnesis of patients with non-melanoma skin cancer (BCC, SqCC) admitted to the Department of Dermatology, of Semmelweis University and also assesses whether HCTZ use imposes an enhanced risk of NMSC.

Methods: Throughout 2019, a case-control study was conducted on patients whose therapy was managed in our Department of Semmelweis University. The study compared patients with non-melanoma skin cancer (BCC, SqCC) with cancer free subjects, who were also HCTZ users.

Results: Over the period 847 patients have undergone surgical procedures, 657 of whom suffer from basal cell carcinoma (BCC) and 190 from squamous cell carcinoma. Those subject to HCTZ treatment after operation amount to 68 in the BCC group and 38 in the spinalioma group. 66 patients of the 1139 numbered control group receive HCTZ treatment, this concludes an odds ratio of 1.87 (95%CI: 1.31 to 2.6) in case of the BCC group and an OR=4.06 (95%CI: 2.63 to 6.27) for the spinalioma group.

Conclusion: In support and confirmation of EMA's safety consideration on medicinal products with the active ingredient hydrochlorothiazide, the study served to justify that an increased risk to developing NMSC can be distinguished among patients on long term treatment of HCTZ.

A pharmacist-led, prospective audit on antibiotic prescribing at traumatology ward

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Background: Our institution commenced a pharmacist-led antimicrobial stewardship service at 3 hospital wards in September 2018. After the 3-month pilot phase we extended the service to the traumatology ward.

Aims: Our aims were to document and analyse the prescribed antibiotic therapies, as well as to record the clinical pharmacist interventions and the rate of acceptance.

Methods: The prospective, interventional study was started in January 2019, and has been performed over an 11-month period. Baseline patient data, documentation of allergies, indication of therapies and circumstances of microbiological testing were collected on a paper-based audit form. Patient charts and medical records were applied as data sources. Detailed information on antibiotic therapies and the 48-72-hour revision with outcomes were also documented. Clinical pharmacist interventions (CPIs) were categorised and their acceptance were recorded. Microsoft Excel was used for data management and analysis.

Results: 77 patients were involved in our study, 41 men and 36 women (mean age was 57.7 years ± 19.2 years and 72.4 years ± 17.6 years). Overall, 81 antibiotic therapies (59 empirical and 22 targeted) were evaluated. 16 different antimicrobial agents were prescribed, the most frequent was amoxicillin-clavulanic acid (27 cases). Based on the evaluation by the infectologist and clinical pharmacist, 24 cases (30%) of all antibiotic therapies were inappropriate. Initial antibiotic therapies weren't optimal in 21 cases (26%), mainly due to the unnecessary initiation of antimicrobials in asymptomatic bacteriuria before orthopedic procedures (38% of initial inappropriate therapies). Therapeutic decisions at the revision

point were inappropriate in 28 cases (35%). CPIs were actioned in 36 cases, most frequently discontiunation of the therapy (43%) and parenteral-oral conversion of the therapy (25%). The overall rate of acceptance was 64%.

Conclusion: The audit plays a crucial role to highlight inappropriate practice on antibiotic prescribing and gives the opportunity to the clinical pharmacist to provide continuous and prompt feedback to the prescribers. Their different professional insight can further improve appropriate antibiotic usage.

Anticancer activities of herbal sesquiterpenes of *Neurolaena lobata*

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Background: Cervical cancer is a leading malignancy in women mainly with underlying *human papillomavirus* (*HPV*) infection.

Aims: Sesquiterpene constituents of *Neurolena lobata L. (Asteraceae)* were tested on human cervical malignant cell lines in vitro in order to evaluate their antiproliferative, antimetastatic and proapoptotic effects.

Methods: The antiproliferative effects were investigated with the MTT assay, IC50 values were determined on three cervical cancer cell lines with different *HPV* status (SiHa, HeLa, C33A). Tumor selectivity was examined by using fibroblast cells (NIH, MRC-5). The migratory capacity of tumor cells was analyzed by the wound healing assay, the migration of the cells into the wound site was visualized by phase-contrast inverted microscope. Images were taken by a CCD camera at definite intervals and the rate of migration was calculated according to the rate of wound closure by ImageJ software. Invasive features of the cells were investigated by Boyden-chamber assay on HeLa cells. The number of cancer cells that invaded the Matrigel-coated membrane were assessed after crystal violet staining under phase-contrast microscope. Cell cycle analysis was performed by flow cytometry in order to further elucidate the antitumor effects of the tested sesquiterpenes.

Results: Two of the twelve tested compounds showed pronounced antiproliferative effects with significant tumorselectivity IC50 values varied between 1.83-8.14μM). SiHa, an *HPV* 16-positive epithelial cervical cell line was the most responsive to the treatment. LOB-48, the most effective sesquiterpene component inhibited the cell migration and invasion in concentration dependent manner. According to the cell cycle analysis, LOB-48 slightly elevated the cell number in the hypodiploid phase and altered the distribution of the different subpopulations.

Conclusion: Our results revealed the in vitro antitumor effects of sesquiterpenes isolated from Neurolaena lobata and confirm its proper utilization in traditional medicine as an anticancer drug. The tested sesquiterpene constituents can be candidates for the design of new anticancer agents.

Chemotherapy extravasation management

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Background: Extravasation of chemotherapy which is defined as the accidental leakage of anti-cancer drugs from the vein into the surrounding tissue at the injection site and can result in severe and irreversible local injuries. Multiple factors play a role in the potential occurrence of extravasation, including the volume, contact time, antineoplastic agent properties and individual patient characteristics, such as the condition of peripheral veins.

Aims: The main goal of our present work was to improve patient safety and medical care by reducing the risk of extravasation, to provide evidence-based guidance on all aspects of extravasation and educate staff consistently on early preventative measures.

Methods: Local protocol for the prevention and management of extravasation is in accordance with the latest scientific literature.

Results: Providing an extravasation kit, available at the ward, and by implementing guidelines in the practice setting, nurses' up to date knowledge in the treatment of intravenous cytotoxic chemotherapy is ensured. The extravasation kit – provided by the pharmacy – contains documentation forms, such as instructions for use, extravasation form, antidotes and other necessary materials (e.g. sterile syringes, cannulas, cold-hot packs) for the immediate management of a chemotherapy extravasation.

Conclusion: Keeping in mind that the most important approach in order to minimize the consequences of extravasation is prevention, it is crucial that an extravasation is recognized and diagnosed promptly, since delays in the treatment increase the risk of necrosis. Hence patient awareness, modern port devices, medical team experience and the presence of clinical pharmacists play a key role in reducing frequency and severity of extravasations.

Antibacterial activity of domestic acacia, lime and sunflower honeys

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Background: With the unnecessary and irresponsible use of antibiotics the incidence of resistant bacteria strains has increased nowadays, hence also in Hungary, antibiotic resistance poses one of the highest patient safety risks. Honey has been confirmed to inhibit bacteria proliferation, thus it can provide an alternative solution for the treatment of resistant infections. The antibacterial effect of honey is mostly attributed to the presence of H_2O_2 and the bacteriostatic properties of the antioxidant compounds. A large proportion of bacterial infections are due to the formation of biofilms, which need to be reduced or destroyed in order to ensure the effectiveness of the treatment.
Aims: The aims of our research were to verify the botanical origin of the unifloral honey varieties and to determine the extent to which the botanical origin influences their antimicrobial effects, including their anti-biofilm activity.
Methods: The exact botanical origin of the unifloral honeys (purchased as acacia, sunflower and lime honey) was determined by means of microscopic pollen analysis. The antimicrobial effects against bacteria causing upper respiratory tract infections (e.g. *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Haemophilus sp.*) were tested by in vitro microbiological methods. Our pilot experiments were carried out with agar diffusion test, then the biofilms were cultured on 96-well polystyrene microtitre plates and the inhibitory effect of honey on bacterial biofilm formation was revealed with crystal violet assay.
Results: Microscopic pollen analysis confirmed the botanical origin of the various honey samples, the tested honeys corresponded to the variety indicated on the packaging. Different honeys inhibited bacterial growth to a different extent in the pre-experiments, and we received similar results also in hindering biofilm formation. The degree of inhibition was influenced by the composition and botanical origin of the particular honey types.
Conclusion: It has been observed that the tested unifloral honey varieties were able to reduce the biofilm formation in case of a number of bacteria involved in respiratory infections. The introduction of honey, complementary to antibiotics can have a significant role, as it achieves its antibacterial effect on several points of attack.

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The usage of topically administered corticosteroids and their dilutions in different creams and ointments in the Hospital of Szekszárd

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Background: Certain dilutions of topical corticosteroids are part of the most often used treatments in the Department of Dermatology at the Hospital of Szekszárd. These ointments and creams have anti-inflammatory, vasoconstrictive and antiproliferative effects. Due to these properties, "topical steroid dilutions" are used to treat allergic contact dermatitis, psoriasis, atopic dermatitis (eczema) and intertrigo. Physicians prescribe in our region corticosteroids diluted with different types of ointment bases so in spite of the lack of this topic's popularity, it would be really necessary to emphasize its importance.
Aims: The aim of this study is to help dermatologists and pharmacists find their way amongst the uncountable variations of "topical steroid dilutions" by discussing the mixtures used in our Hospital.
Methods: Consultation with dermatologists, reviewing of both English and Hungarian literature, collection and analysis of prescriptions of community pharmacy Ezüst Kígyó.
Results: During the data collection we found that not only the concentrations of these mixtures vary but they are also prescribed in many forms (pastes, ointments, creams, etc.). The most often used vehicle is Cremor refrigerans FoNo VII. The physicians prescribe one or two tube topical corticosteroid (Flucinar, Elocom, etc.) with Cremor refrig grammata 100 or ad grammata 100/200. Sometimes are used borax in order to killing germs. There is a pasta with one tube Elocom to treat the intertigo. A pediatrist prescribe a mixture with Ung. hydrophil. nonion, Ung. emolliens and Advantan 1:1 ratio. To the better penetration physicans use Unguentum glycerini and stearini, sometimes Acidum salicylicum or Ung. ad vulnera FoNo VII. in different concentrations.
The success of the treatment depends on many factors such as the skin problem, the properties of the semi-solid bases that the prescribed corticosteroids are mixed in and the duration of the treatment. According to the latest reports the dilution of ointments containing corticosteroids does not reduce the risk of adverse effects and we also have to consider the fact

that without related clinical studies we can not be certain of the presence of molecular interactions within these new compositions. When it comes to dispensing medications, pharmacists should focus more on providing relevant information to the patients at community pharmacy – in relation to certain preparations. Consulting with dermatologists would be really important in order to clarify any upcoming uncertainty when dispensing these diluted preparations.

Conclusion: Due to the lack of evidence based knowledge in this field we can say that these dilutions of topical corticosteroids are presumably not the best option to treat cutaneous diseases, but years of medical experience seem to prove that some of these preparations have their role in dermatological treatments. But sometimes the best way is applying creams of FoNo as moisturizing products and than the topical corticosteroid in monotherapy.

Quality by Design-based development process of resveratrol-enclosing intranasal liposomes

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Background: Resveratrol, a polyphenolic stilbene, is under investigation to be used for the prevention and treatment of Central Nervous System (CNS) diseases (Parkinson's and Alzheimer's disease) due to its antioxidant property [1]. The chemically unstable compound has poor water solubility and can easily degrade by high temperature, UV lights, pH changes, and enzymes. However, the enhancement of its absorption by the use of liposomes can be an overcome on the low oral bioavailability, delay the drug release and reach better stability. Intranasal application, as an alternate 'nose-to-brain' administration route, means a way to reach the brain without the limitations of the blood-brain barrier. The application of the Quality by Design (QbD) method, a new quality management procedure, is adopted more and more times in the field of pharmaceutical developments to rationalize the study design [2].

Aims: Our research goal was to establish a development process for a liposomal resveratrol-containing formulation for brain target and nasal administration. Our work presents how to apply the risk-focused QbD approach in the development phase of a research project.

Methods: By the application of the QbD-based approach, the quality target product profile was defined, the critical factors were selected and a risk assessment (RA) was performed. Based on the results of the RA, the liposome preparation (lipid-film hydration method) was designed and the necessary instrumental investigations to check the process were planned.

Results: The determination of the important features and parameters (QTTPs, CQAs, and CPPs) provides a holistic network of information that can be useful to achieve a more effective experimental design.

Conclusion: The results proved that the collection of the proper information combining with the optimization and the rationalization of the required experiments and measurements can improve the development process of the liposomal formulations.

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Results of antibiotic policy development at the National Institute of Clinical Neuroscience

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Background: Antibiotic Policy (AP) of the National Clinic of Neuroscience (OKITI) was approved in 2011. In recent years, antibiotic use has been steadily increasing in both days of treatment (DOT) and value cost. The reasons for the increase and the necessary measures were taken in spring 2018 on the recommendation of the Institute for Infection Control and Antibiotics (IIAB). One major change in Antibiotic Policy is the renewal of the antibiotic prescription sheet. The purpose of the poster is to present the results of the period since the introduction of the Antibiotic Policy on May 1, 2018.

Aims: Description of OKITI AB policy owing to improvement of antibiotc therapy.

Methods: Evaluation of OKITI antibiotic use, and processing of antibiotic prescription sheets.

Results: Close cooperation between IIAB members. We were able to control antibiotic orders with the help of a hospital-based infectologist. A pharmacist checks and dispense the antibiotics. As a result of this collaboration, we have been able to stop the increasing use of antibiotics (both both days of treatment and in value) for years. Following the recommendation of the European Medicines Agency (EMA), the use of fluoroquinolone has decreased at institutional level (only an infectologist can initiate fluoroquinolone therapy).

Conclusion: Antibiotic use (in value cost) is a significant part (10 %) of the cost of medicine for hospitals. A well-working antibiotic management team can streamline usage, reduce costs, and stop the rise in antibiotic resistance.

Experiences of implementing antimicrobial stewardship in the University of Debrecen

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Background: In the last two decades the emergence and spread of antibiotic resistance, in other words the ability of bacteria to resist the action of an antibiotic, has become a recognized global problem. Antibiotics are frequently used inappropriately or when they are not needed.
Aims: The primary goal of antimicrobial stewardship is to optimize the use of antibiotics to prevent the development and spread of antibiotic-resistant bacteria and improve clinical outcomes.
Methods: Based on Regulation No 32/2018, the Institutional Infection Control and Antibiotic Committee has determined the list of controlled antibiotics and the multidisciplinary team in charge of antibiotic stewardship was established. 21 out of 47 antibiotics used in Clinical Centre are regulated the physician, the infectologist, the microbiologist, the clinical pharmacist and the representative of management are responsible for the operation of the system. Certain antibiotics can only be used documented approval by the infectologist. It is compulsory to fill out electronic forms to order the restricted antibiotics and after the therapy is over. Antimicrobial pharmacist as key person supervises the therapy including dosing, interactions, incompatibilities and drug allergies to ensure adequate therapy. Members of the antibiotic stewardship team assess the cases, oversee adherence to the local protocol, evaluate the antibiotic consumption (DDD) and monitor the changes of bacterial resistance. The results provide information for further intervention.
Results: Rationalizing the use of antibiotics was successful. Antibiotic prescribing practice, the local resistance conditions and the cost-efficiency were changed which confirm the necessity of antibiotic stewardship.
Conclusions: With the help of evidence-based antibiotic use, therapy can be optimized, and hospital costs can be decreased. The system contributes to preventing development of antibiotic-resistant bacteria and save the efficacy of antibiotics.

Comparative study of the *in vitro* toxicity of artificial tears and ophtalmic preservatives in a human conjunctival cell line

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Background: Dry eye disease (keratoconjunctivitis sicca, KS) is one of the most common ophthalmic diagnoses. Although the development of KS does not lead to the development of a life-threatening condition, it can significantly impair the patient's quality of life and thus his or her ability to work. In many cases, the composition of KS formulations is determined by market needs rather than by strict professional expectations. There is currently no study comparing the cytotoxicity of artificial tears and their preservatives in community pharmacies on a conjunctival model.
Aims: The aim of our work was to set up a new in vitro experimental model that can compare artificial tears and their preservatives, thus helping the daily work of professionals. As well as analyzing national sales of artificial tear.
Methods: The effects of various treatments were investigated in vitro using the MTT assay on the Chang CCL-20.2 human conjunctival cell line. We compared our results with national sales of teardrops.
Results: As a result, the formulations and their preservatives can dramatically affect the viability of the Chang CCL-20.2 human conjunctival cell line. Analysis of sales data pointed to a serious deficiency in pharmacy patient information.
Conclusion: Based on our findings, many of the currently available artificial tears may cause a long-term risk to patient's health. Therefore, it would be important to review them and optimize their composition.

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The effect of restrictions on fluoroquinolone anitbiotics usage in hospital care

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Background: In 2019 EMA's human medicines committee (CHMP) confirmed that the use of the fluoroquinolone (FQ) antibiotics should be restricted because of disabling and potentially permanent side

effects. Hungarian National Institute of Pharmacy and Nutrition (OGYÉI) released in April 2019 direct healthcare professional communication (DHPC) for safer use of fluoroquinolone antibiotics and all Summary of Product Characteristics (SPCs) were revised.
Aims: Monitoring and improving fluoroquinolone antibiotics usage in the Buda Hospital of the Hospitaller Order of Saint John of God (Budai Irgalmasrendi Kórház) regarding changes in SPCs and DHPCs.
Methods: Analysis of fluoroquinolone antibiotic usage in the hospital, especially in those units where FQs are frequently used. We made a retrospective analysis of patient documentation before and after DHPC release whether FQ usage was appropriate. We designed a questionnaire to collect all relevant information.
Results: Results show that despite the restrictions on indications, the usage of FQ antibiotics in our hospital is still high. We believe that DHPCs alone may not be effective enough to change strong prescription habits.
Conclusion: We decided to do some training for prescribing doctors to reach appropriate fluoroquinolone antibiotics use, to improve patient safety, save cost and disburden the nurses with the timely switch from parenteral to oral dosage form.

Development and characterization of human serum albumin glycoconjugates containing biopolymers

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Background: Proteins, due to their interfacial structure, are widely used as emulsifiers in the food industry and are gaining interest in the pharmaceutical research. However, proteins are very sensitive to environmental stresses, protein glycoconjugates has improved functional properties such as emulsifying ability, thermal stability and foaming capacity. Glycation, commonly known as Maillard reaction, is a simple, spontaneous and naturally occurring „green" reaction. This non-enzymatic conjugation takes place between reducing sugars and available amino groups of a protein in certain conditions of temperature and humidity. Human serum albumin was chosen as model protein due to its importance in the modern drug delivery systems nowadays. Biopolymers such as polysaccharides derived from plants are widely used in due to their biocompatibility and safety.
Aims: The aim of this study was to prepare glycated human serum albumin with branched and linear chain polysaccharides such as galactomannan (locust bean gum, LBG) and sodium alginate (ALG). The glycated products were further characterized using fluorescence spectroscopy, gel electrophoresis, DSC, XRD and FTIR, furthermore, emulsifying ability was also tested.
Methods: The human serum albumin and biopolymers were added together in distilled water in 1:1, 1:2, 1:3 and 1:6 molar ratios and freeze dried in order to remove water. After that conjugates were prepared by at 60°C and 80% relative humidity for 72 hours.
Results: The Maillard reaction between HSA and polysaccharides was verified by fluorescence spectroscopy. The intensity of amine IR absorptions was increased while that of the amide I and II bands were significantly decreased on the specta of HSA conjugates which is more prominent at the 1:6 molar ratio. The fluorescence emission intensity of Trp 212 residue of HSA was significantly decreased on the specta of both conjugates due to the conformation changes of the protein.
Conclusion: It can be concluded that glycation was successful and the potential use of Maillard reaction in pharmaceutical industry could be assumed.

Histological evaluation of plants based on ethnomedicinal data in Transylvania

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Background: Although medicinal plants are of primary importance in many regions of Transylvania, we have little information on the histological traits of their drug parts. Based on earlier ethnomedicinal surveys (2007-2019) in Transylvania, four plant species were selected for complex analyses including histological investigation of their parts applied in traditional treatments.
Aims: Our goal was to provide anatomical data of the medicinally important organs of *Anthyllis vulneraria L.*, *Lathyrus tuberosus L.*, *Lysimachia nummularia L.*, and *Tanacetum balsamita L.*
Methods: Plant samples were collected from the typical habitat of each species. Preceding embedding in artificial resin, samples were dehydrated in ascending ethanol series. Cross sections were cut with a rotary microtome, and stained with toluidine blue. Light microscopic investigation was performed with a Motic 102M microscope, and micrographs were taken with Motic Images Plus 2.0.
Results: The tuber of *L. tuberosus* is covered by periderm, below which groups of sclerenchymatous cells are scattered. A substantial portion of the tuber is filled with nutrient storing parenchyma. The cylin-

drical stem of *A. vulneraria* is characterised by the presence of vascular bundles in addition to continuous vascular tissues, a significant portion of pith parenchyma and the presence of calcium oxalate druses. The petiole contains four minor and a single central vascular bundle, the latter one supported by sclerenchyma. The dorsiventral leaf bears uniserial, non-branching cover hairs on the abaxial side. Mesomorphic stomata are located on the adaxial surface. The cross section of the stem in *L. nummularia* is four-cornered; the epidermis is formed by circular, isodiametric cells with papillae, thickened cell walls and cuticle; and vascular tissues form a continuous ring. Mesomorphic stomata and capitate glandular hairs appear on both sides of the dorsiventral leaves. Essential oil cavities can be observed in the mesophyll. The dorsiventral leaves of *T. balsamita* are characterised by the presence of capitate glandular hairs, which are responsible for essential oil secretion.

Conclusion: Our research provided the first detailed histological description of the drug parts of four medicinal plants widely used in Transylvania. Our results can contribute valuable data also to the phytochemical studies of the species, by revealing the exact site of active compound synthesis.

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Comparative ethnomedicinal survey in the Homorod Valley, Transylvania

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Background: Homorod Valley, region of Székely Land in Transylvania has been studied for ethnobotanical data earlier (e.g. Gub 1994) documented the traditional knowledge of Székely people of 14 villages.

Aims: The aim of our work was to collect and compare ethnomedicinal data obtained from 10 villages of Homorod Valley. In data comparison, similarity and differences were taken into consideration.

Methods: Ethnobotanical survey was conducted in Aldea, Bădeni, Călugăreni, Comănești, Ghipeș, Locodeni, Mărtiniş, Petreni, Sânpaul, and Orășeni (2013-2019). These settlements are 2-15 km far from each other belonging to Mărtiniş as region centre. Semi-structured interviews were performed with ~150 informants aged from 14 to 99. Interviews focused on the local name, collection time and place, used parts, preparation and administration, as well as treated disorders of plants based on traditional elements. Data were arranged in tables comparing terminology, application and indications of the mentioned plants in each village. In addition, our records were compared to those of earlier works to indicate overlapping, disappeared and new records. Plants were also compared to medicinal plants of Pharmacopoeia Hungarica VIII (Ph. Hg. VIII) to highlight scientifically proved data.

Results: Total number of records of plants varied from 42 to 73/village. Altogether 12 plants were described as overlapped species in all settlements, and 36 ones official in Ph. Hg. VIII (e.g. *Achillea millefolium*, *Calendula officinalis*, *Plantago lanceolata*). Some species were documented only in 1-1 village, e.g. *Lamium album*, *Morus alba* (Mărtiniş), *Echium vulgare*, *Orchis morio* (Sânpaul), *Helleborus purpurascens* (Orășeni), and *Atriplex hortensis* (Aldea). Altogether 10 plants were mentioned of other origin, e.g. of books and media sources (e.g. Capsella bursa-pastoris, *Silybum marianum*, *Melilotus officinalis*), and 3 new species cultivated from urban environment (Aloe sp., *Lavandula angustifolia, Rosmarinus officinalis*). Compared to earlier data, majority of our records overlaps with those published in 1990s. Among disappeared records, e.g. use of *Aegopodium podagraria, Daphne mezereum*, and *Inula helenium* can be mentioned.

Conclusion: This survey underlines the importance of ethnomedicinal collection in this region, and of data comparison as a case study in ethnobotanical researches.

This work was supported by a grant from the OTKA (Hungarian Scientific Research Fund, K 127944).

Reference: Gub, J. Néprajzi Látóhatár, 1993;1-2:95-110.

The treatment of anhedoniae with antidepressants and ketamine

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Background: Anhedonia is one of the main symptoms of depression, which is generally associated with a decreased ability to feel joy and pleasure. It affects approximately 37% of people with depression and it has different triggers, thus bit's manifestation can be different from patient to patient. Anhedonia is relatively difficult to treat, most antidepressants currently in use are ineffective.

Aims: In most cases, the widely used SSRI treatments are ineffective, often aggravate depressive symptoms. There are new suggestions for ketamine

therapy, which is an antagonist of the NMDA receptor and has an anti-depressive effect. Several studies have mentioned ketamine to treat the symptoms of anhedonia, especially in case of decreased ability to feel pleasure there are also several evidences suggesting that substances that are targeting the glutamatergic system and affect the level of norepinephrine and serotonin are helping in the recovery from anhedonia.

Methods: I have reviewed the latest articles on anhedonia treatment and extracted the relevant results.

Results: The most studies treatment are ketamine, imipramine, fluoxetine, clozapine, and haloperidol. A study approved that fluoxetine had no effect on anhedonia, and while imipramine therapy showed effectiveness but only on certain subgroups of rats that were exposed to chronic stress. The treatment of clozapine had an effect on anhedonia but did not improve the hyporeactivity. Haloperidol also had no influence on the symptoms of anhedonia. Ketamine is proved to be effective but in many cases, there are side effects.

Conclusion: It is hard to find the perfect treatment because the level of anhedonia can be very different among people. There are good approaches in various articles, but there are still not clear enough for targeted therapy. First, we have to find an animal model that is better suited to human anhedonia. In the next step, we need more animal experiments to find new targets, but this is still a hard task. We still do not know enough about anhedonia to find the perfect treatment. Ketamine is a step in the right direction, but we need further research.

Cytotoxicity investigations of different polyethylene glycol (PEG) derivatives

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Background: Polyethylene glycol (PEG) polymers are hydrophilic, water miscible and can solubilize many poorly water-soluble compounds. This compound has variety of applications from chemical manufacturing to medical field, depending on their molecular weight, especially in pharmaceutical industry as an excipient. PEGs are available commercially with wide molecular weight range from 200 to 10.000.000.

Aims: The aim of this study was to investigate the cytotoxicity of PEG with different molecular weight.

Methods: My experiments were performed on the Caco-2 human adenocarcinoma cell line by cytotoxicity assays including MTT and neutral red (NR) methods. They were implemented with different concentration of various PEG derivatives (based on molecular weight).

Results: PEGs with differrent molecular weight were examined at concentrations of 2%, 10%, 30% and 40%, respectively. All tests were carried out with both MTT and NR methods. The cell viability was high at 2% concentration and slighlty decreased to 70% at 10% and 30% concentrations. Finally, PEGs were seriously harmful to cells when increasing the concentration to 40%. The cytotoxicity was elevated to 50% and above at this concentration.

Conclusion: PEG are relatively nontoxic in increasing concentration to 30%. PEGs have severe effect on cell PEG if the concentration is above 30%. According to our results, we can say that PEGs are a good choice for new drug formulation because of their safety. Therefore, PEGylation has become a promising method for the delivery of traditional drugs and biopharmaceuticals due to its bioavaibility improving effect.

Study on interaction of some (E)-2-benzylidenebenzosuberone derivatives with serum albumin by spectroscopic methods and on topoisomerase inhibition

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Background: Some cyclic chalcone analogues, (E)-2-(4-X-benzylidene)-1-benzosuberone derivatives showed remarkable biological activity including tumor citotoxic effect.

Aims: Based on preliminary results, the biological activity of the compounds might be partially th result of non-covalent interaction between the compounds and cellular macromolecules (proteins, DNA). For a better understanding of the mechanism of action, interaction with different proteins was investigated.

Methods: The UV-Vis absorption spectra of bovine and human serum albumin titrated by selected (E)-2-(4′-X-benzylidene)-1-benzosuberones analogues solution were monitored in order to explore the structural changes of BSA and HSA caused by addition of the compounds. Their effect on the activity of the nuclear enzyme DNA topoisomerase I and II was also investigated.

Results: The results suggest a non-covalent interaction between the compounds and serum albumin, which occured via the π-π stacking between aromatic rings of chalcone analogues, and Trp residues possessed conjugated π-electrons and located in the binding cavity of serum albumin. The investigated derivatives showed weak dual inhibitory activity against DNA relaxation by topoisomerases I and II.

Conclusion: The interaction with protein and the observed moderate topoizomerase inhibitory effect might be contributing vectors of the observed cytotoxicity. The obtained results provide additional knowledge on pharmacological effect of cyclic chalcone analogues.

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Vapor chamber, a novel method for rat liver perfusion in metabolite research

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Background: Hepatic steatosis in obese or non-obese patients may alter drug metabolism. As an ex vivo simulation model, isolated rat liver perfusion is used for the examination of the liver metabolism. This method has several advantages, such as the architecture of the organ is saved, compare to in vivo model higher dose of drugs can be tolerated and large number of perfusion samples can be collected.
Aims: To investigate the possible alterations of drug methabolism in hepatic steatosis. To develope a new method for rat liver perfusion (ex vivo).
Methods: After the cannulation and removal, the liver of male SPRD rats (300-320 g) was placed into the porous chamber filled with buffer vapor. Oxygenated perfusion buffer was pumped into the organ in a recirculating pattern with constant flow rate. The pressure and pH of perfusion fluid were controlled during experiment continuously. In order to monitor the liver viability, the lactate dehydrogenase (LDH) level was determined in collected samples. The liver function was investigated by pharmacokinetics determination of diclofenac (DF) and its main metabolites via targeted reversed-phase LC-MS/MS method.
Results: The viability of the perfused liver was around 2-4 hours based on the measured LDH level (max. 300U/l) in the perfusion solution and the amount of the produced bile (3-6µl/min). The dynamic alterations of the concentrations of 4′-hydroxydiclofenac (Phase I. metabolite), and diclofenac-1-O-acyl glucuronide (Phase II. metabolite) were determined in the perfusion fluid. The amounts of Phase I and Phase II metabolites were 7.7 and 11.7 folds higher, respectively at 100min as compared with at 10min after starting the perfusion.
Conclusion: A new rat liver perfusion method was successfully developed. The novelty of the method is the lack of hydrostatic pressure on the liver that may provide a more physiological condition for the organ as compared with former methods. This method seems to be proper for the investigation of drug metabolism in different hepatic conditions, including the obesity induced hepatic steatosis.

The effects of leptin, adiponectin and kisspeptin on pregnant rat uterine contractility *in vitro*

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Background: It is generally accepted that several adipocytokines are regulators of the reproductive system, since they influence the hypothalamic-pituitary-gonadal axis. Their plasma concentrations have been found to alter during gestation and it is also hypothesized that they take part in pregnancy related complications.
Aims: The aims of this study were to clarify the uterine effects of leptin, adiponectin and kisspeptin on different gestational days in pregnant rats and to identify the myometrial and uterine expressions of their receptors throughout pregnancy.
Methods: KCl-induced contractions of uterine rings from pregnant Sprague-Dawley rats were measured in an organ bath on gestational day 5, 15, 18, 20 and 22. Cumulative dose-response curves were elicited in the presence of leptin (10^{-12}–10^{-8}M), adiponectin (10^{-12}–10^{-8}M) or kisspeptin (10^{-12}–10^{-7}M). The isolated organ bath experiments were also carried out after endometrial removal. The myometrial and endometrial expressions of the adipokine receptors were determined by RT-PCR and Western blot analysis.
Results: We found that the uterus relaxant effect of leptin was strong at the early phase of pregnancy, but it decreased towards the end of gestation. We observed a similar trend in the case of kisspeptin, but its inhibitory effect was still detectable on the 22nd day. The relaxing effect of adiponectin tends to increase from pregnancy day 5 to day 18, but then practically ceases on the last day of gestation. The removal of the endometrium altered the uterine relaxant effects and the expressions of receptor mRNAs and proteins in the uterus.
Conclusion: All the investigated peptides inhibited the contractions of pregnant rat uterus. The effects of leptin and adiponectin ceased towards the end of pregnancy, suggesting that they had no crucial role in the last day contractions. On the other hand, kisspeptin had significant relaxing action during the whole pregnancy. The myometrial and endometrial expressions of the adipokine receptors were confirmed as well.

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Utilization of asthma and COPD medications in Hungary between 2008 and 2018

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Background: The prevalence of asthma and chronic obstructive pulmonary disease have considerably grown in Hungary during the past decade.
Aims: Our aim was to analyze the utilization of medicines used for the treatment of obstructive airway diseases (asthma and chronic obstructive pulmonary disease) and their financial burden between 2008 and 2018.
Methods: Data was collected from the National Health Insurance Fund of Hungary containing the reimbursed medication use of the entire population. Data was analyzed using the WHO's ATC/DDD system and expressed in Defined Daily Dose per 1000 inhabitant per day (DDD/TID).
Results: The total use of drugs for chronic obstructive airway disease (ATC: R03) increased from 33.27 DDD/TID in 2008 to 42.30 DDD/TID in 2018. In 2008 the most frequently used medicines were the xanthines with 9.96 DDD/TID, and by the end of the study period their consumption decreased by 29% to 7.08 DDD/TID. In 2018 the most popular drug group was inhaled corticosteroids in combination with long acting beta2-agonists which use rose by 56% from 6.41 DDD/TID in 2008 to 9.98 DDD/TID in 2018. During the study period the total drug expenditure showed a 36% increase reaching 95.1 million Euro in 2018.
Conclusion: As the prevalence of chronic obstructive pulmonary diseases increased the utilization of drugs used for their treatment increased as well. The utilization of preparations containing combination of inhalation medications showed the highest increase during the study period.

The level of mercury in thermal waters

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Background: Thermal waters are the most used in our century for different types of skin. The biggest advantages of the thermal waters are naturally antioxidant, soothes and protects, moisturizes and make a stronger barrier for healthier looking skin. The consumer could use a big quantity of this type of dermatocosmetic daily.
Aims: Our study aims to discover if a quantity of this products could be high level of mercury potential hamfull for skin [1,2].
Methods: A total of 6 samples of thermal water from commercial brands were selected from beauty shop and pharmacy. The equipment used to analyze this samples is AMA 254 Mercury Analyzer (Leco, Czech Republic) which measure mercury concentration in products.
Results: The values of mercury in samples on the market are under the limits allowed by the European Union. The consumer could use a bigger quantity of thermal water than regular cosmetic products and even if the level of mercury is under the limits these products could be a potential risk. But the amount of mercury in thermal waters is in lower concentration to the amount of mercury when exposed to air or even drinking water.
Conclusion: Most cosmetic products have a higher concentration of mercury than thermal water sprays. These thermal waters even if applied to the skin several times per day, they are not a potential risk for our skin's health and safety. When using thermal waters in combination with many other cosmetics, including make-up products, caution is advised as all those products combined may lead to an increase of mercury levels in the body.

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QbD-based formulation of intranasal polymeric micelles

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Background: Polymeric micelles offer a great way to improve bioavailability, water solubility and the toxicological profile. They can be applied through alternative administration routes such as intranasal targeting the central nervous system directly. Quality by Design is a novel approach in research and industry, therefore it can be applied in the early stages of pharmaceutical developments as well.
Aims: Our goal was to formulate NSAID-loaded polymeric micelles with proper particle properties, material structure and in vitro characteristics which can be used for intranasal administration treating the inflammatory responses in the CNS.
Methods: At first, QTTPs, QCAs and CPPs were determined and a risk assessment was evaluated in

harmony with the ICH guidelines. For API we used Meloxicam and tocophersolan as a micelle-forming amphiphilic graft co-polymer. The formulation is based on solvent extraction and precipitation. We used a 3-level Box-Behnken factorial design to optimize the formulation. We investigated the particle size, polydispersity index, zeta-potential as main three nanoparticle determining parameters. For the material structure investigations, we used XRPD, DSC, TG and spectrophotometric measurements. The encapsulation efficiency was measured via HPLC. In vitro dissolution and permeability studies were carried out in SNES media. The physical stability was investigated monthly after freeze-drying and storing at 5±3°C.

Results: We successfully determined and optimized the main factors using QbD methods for the desired quality. The products show us monodisperse distribution with proper zeta-potential and particle size even after storing for months. The characteristic peaks of the API or the polymer cannot be detected in the products, the material structure investigations indicate that it has amorphous crystalline structure. The in vitro kinetics and the encapsulation efficiency showed us good results which correlates with the criteria of the intranasal administration.

Conclusion: The stable polymeric micelles with the proper quality and quantity parameters can be used for intranasal administration. Quality by design can be applied in researching nanotechnology-based drug delivery systems as well. Tocophersolan can be used as a polymeric micelle-forming excipient.

Potential immunotherapy target identification in glioblastoma and meningioma

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Background: Despite relentless research, survival rates of malignant tumors of the central nervous system (CNS) have not improved significantly. Glioma is categorized as low grade glioma and higher-grade glioma. Glioblastoma (GBM) is the aggressive malignant glioma. In contrast, meningioma is a slow growing, more benign brain tumor originating from the meninges, but can be recurrent and even turn malignant. The primary therapy for both tumor types is surgery and radiotherapy. Temozolomide (TMZ) can increase survival rates, but not all CNS tumors are responsive to TMZ.

Aims: The current study has focused on the immune microenvironment of two types of brain tumors, namely grade IV glioma and grade I meningioma.

Methods: Tissue samples were postoperative primary CNS tumors, grade IV glioma and grade I meningioma. Using quantitative real-time PCR mRNA levels of characteristic immune cell surface markers (CD3, CD4, CD8, CD56 CD19, CD168 etc.), cytokines (TGFβ, IL10, etc.) and Indoleamine 2,3-dioxygenase (IDO) were determined. Immunohistochemistry supported the presence or absence of specific protein levels.

Results: In both CNS tumor types the immune microenvironment has proved to be highly similar. Both cases the immune suppressive elements were highly elevated. This included the presence of immune suppressive regulatory (reg) T cells (CD4+FOXP3+) and tumor associated macrophages (TAMs). The m-RNA level of IDO was also increased in both types of tumors. The metabolic product of IDO-1 is kynurenine which generates metabolites that enhance the activities of CD4+ FOXP3+ T-reg cells and myeloid-derived suppressor cells. IL-10 and TGFβ were also over expressed in both tumor types. In contrast, differential expression of molecules targeted by immune checkpoint inhibitors was detected. CTLA4 mRNA level was elevated over normal control, while expression of PD-1 and PDL1 varied individually.

Conclusion: Our results show a strong immune suppressive microenvironment in both tumor types. However, individually selected immune checkpoint inhibitors in combination with IDO-1 inhibitors might become alternative treatments for certain brain tumor types, or even refractory meningiomas and chemoresistant glioblastomas.

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High-priority drug interaction list for use in hospital formulary

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Background: Increasing introduction of electronic prescribing and pharmacist-led prescription order validation in Hungarian hospitals demands improvements to computerized interaction screening. Discrepancies between different drug-drug interaction (DDI) ratings are well-documented. In addition to that, over-alerting and lack of practical recommendations make physicians and pharmacists commonly override DDI alerts. Reaching a consensus on an elementary set of interactions would be a great leap forward in improving patient safety.

Aims: To develop a hospital formulary methodology for selection of high-priority DDIs, the detection of which can be considered as a standard of medical informatics software at our institution.

Methods: Literature searches for similar lists and guidelines on selection and implementation of DDI alerts into clinical systems were performed. A decision model has been developed to identify and select high-priority interactions. As the final list must be achieved by multidisciplinary consensus, candidate DDIs and management recommendations will be discussed by the institutional drug and therapeutics committee.
Results: According to a validated decision algorithm, candidate interactions should be evaluated by the following criteria: evidence, severity of the adverse event, necessity of medical intervention, difficulty of surveillance, availability of suitable alternatives and dose adjustment guidelines, risk-benefit ratio of the combination [1]. Main sources of candidate interactions include (a) consensus-based lists identified in a previous systematic search of the literature [2], (b) DDI databases using a transparent and management-oriented classification system and (c) available evidence-based clinical guidelines on the management of DDIs. Priority should be given to population-based studies as they provide clinically relevant information and are incompletely referenced by DDI databases. Complementary sources include summaries of product characteristics and CYP enzyme databases.
Conclusion: The problem today is not the lack of information on DDIs but to optimally translate it to clinical practice. The presented methodology provides a professionally valid approach for the institutional consensus-based screening of high-priotrity drug interactions in a unit-dose distribution system.

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Clinically significant drug-drug interactions in hemodialyzed patients

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Background: Drug interactions mean interference between drugs, or drugs and environmental factors. Due to such interactions pharmacokinetics may be altered, which modify the expected effects of the medications. Contraindication types of drug-drug interactions (DDI) have outstanding clinical significance, as may cause severe clinical consequences, therefore need special attention when prescribing complex therapy for patients.
Aims: In Szent Margit Hospital Taraba István Hemodialysis (HD) Unit we investigated contraindications of medication therapy in 101 HD patients. Mean age was 69±12 years, 54% of them were male.
Methods: By using DDI Medscape interaction checker we found 10 interactions per patient as an average, and among them 2 were contraindications. We summarize the most important groups of contraindications, indicate the mechanisms of elevated risks, the number of cases at risk, and present some examples.
Results: DDI caused elevated risk of high serum potassium 15 patients, e.g. by administering LMWH and ACEI together. Risk of Stevens-Johnson syndrome might be elevated due to allopurinol and ACEI, or ASA and ACEI interactions (20 cases). Conjugates of some drugs, as calcium-carbonate and ASA, or omeprazole and clopidogrel taken in the same time may lead to antagonism (26 cases). Drug toxicity can be caused by coadministration of digoxin and pantoprazole, also by carbamazepine and alprazolam (22 cases). In patients with reduced liver or renal function coadministering amlodipine and simvastatin increases the risk of rhabdomyolysis by 60% (2 patients). Residual renal function may decrease if taking regularly NSAID and ACEI together (32 patients). Very often patients need to take more than one medications influencing the coagulation system to prevent clotting in HD system and due to thrombotic diseases or atrial fibrillation (contraindication with increased bleeding risk was experienced 44 cases).
Conclusion: Recognition of frequent contraindication DDI has outmost importance. Several investigations have proven that almost one third of hospitalizations are caused by potentially preventable side effects of medications or incorrect drug therapy. Advanced age per se is a risk factor for DDI. In HD patients the minimal residual renal function, high number of comorbidities and the large number of prescribed drugs increase the risk of DDI, which monitorization and elimination are significant tasks of the clinical pharmacologist.

Survey of fifth-year pharmacy students' views on the current state of clinical pharmacy, on their future plans and workplace expectations at Semmelweis University

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Background: In recent years, pharmacists have been paying increasing attention to pharmaceutical care in community pharmacies and clinical pharmacy services in hospitals. The latter position, which is becoming widespread in Hungary and in the practice of Semmelweis University, provides an opportunity

to assess, identify, and solve problems in the patients' medication. University pharmacy education also has to adapt to the new tasks, failing which, a discrepancy may develop between the students' perception of the profession and the actual situation, the competences taught and applied in practice.
Aims: The aim of our study was to find out the fifth-year students' perceptions and opinions about hospital-clinical pharmacist work, to assess students' workplace expectations, future plans (with a hospital-clinical pharmacist focus) and explore differences between students' image and reality.
Methods: During the research, Semmelweis University's fifth-year pharmacy students completed a questionnaire developed by our Institute in October 2019. The 20 questions in the questionnaire covered three topics: hospital-clinical pharmacy concepts, workplace expectations and future plans.
Results: 88 students completed the questionnaire. Students considered professional development as a hospital-clinical pharmacist (4.00 points on a 5-point scale), the main profile of the work is drug supply and drug therapy supervision (3.79; 3.84), however, they think that physicians do not treat pharmacists as equal partners (2.13) and students do not feel prepared to work in this field (2.09). The most important of the workplace conditions is a good relationship with colleagues (4.66), an appropriate salary (4.64), an opportunity for development (4.58) and professional appreciation (4.52). 54% of students want to work abroad for a while and about 30% would like to work in a hospital. The most popular area of work is unit-dose dispensing (4.4) and working as a clinical pharmacist in a hospital ward (4.6), as opposed to ordering and dispensing medicine ("speci"; 2.6) or working in the community pharmacy unit ("kispatika"; 2.9).
Conclusion: Our results will help us better understand the prospects of future graduates, which can help facilitate their integration into the hospital-clinical setting and provide a good basis for mapping the impact of fifth-year education on this.

Characterization of acute stress by gastrointestinal and cardiac electromyography in awake rats

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Background: Stress, anxiety, and various neuropsychiatric disorders are often associated with gastrointestinal (GI) symptoms and heart rate changes. The simultaneous detection of the myoelectrical slow-waves of the GI tract with the changes in heart rate and other parameters may provide more accurate information on patients' acute anxiety and psychological status, but such a method is currently not available in the clinical practice.
Aims: Investigation of acute stress response and stress response reducing drugs with simultaneous detection of GI, cardiac, plasma corticosterone and body temperature changes in wakeful rats.
Methods: The sensor was placed under the abdominal skin of male SPRD rats (300-310g) to record simultaneously the GI tract myoelectric signals, cardiac signals, and body temperature. The primer GI records were analyzed by fast Fourier transformation. The rats were also treated with diazepam (5mg/kg) or haloperidol (1mg/kg) intraperitoneally. The changes in plasma level of corticosterone were determined by ELISA.
Results: Acute stress induced a significant increase in the electromyographic signals of each segments of the GI tract, as well as corticosterone plasma levels, body temperature and heart rate of the animals. Diazepam and haloperidol reduced stress-related parameters, except heart rate, as these agents cause tachycardia. The hypothermic action of diazepam masked the body temperature alterations in the treated rats.
Conclusion: Acute stress can be measured with a single sensor for simultaneous detection of GI- and cardiac myoelectric activity, plasma corticosterone levels and body temperature. During psychopharmacological studies in rats, the change in stress level can be accurately followed by GI electromyography that shows good correlation with the changes in stress hormone levels. The other investigated stress parameters did not fully reflect the changes. Our method may open new perspectives in the diagnosis and treatment of psychosomatic disorders.

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The effectiveness of immunotherapy in non-small cell lung cancer based on real-world data

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Background: Nivolumab is a widely used immune checkpoint inhibitor, which is indicated in many solid tumors including metastatic non-small cell lung cancer (NSCLC). The CheckMate-057 clinical trial demonstrated its efficacy compared to conventional chemotherapy in advanced stage non-squamous (adenocarcinoma, ADC) NSCLC. CheckMate-017 trial verified its efficacy in advanced stage squamous cell carcinoma (SCC) NSCLC patients.

It is confirmed that under controlled clinical research conditions, health gain produced by a drug is better than the outcome in the daily therapeutic routine. Health benefit achieved in the daily practice is called the effectiveness of the therapy. Beside efficacy, also effectiveness of a therapy should be considered when quantifying the net benefit of care.

Aims: Our main goal is to obtain real-world evidence about the promising immunotherapy in the therapy of lung cancer. Therefore we measured primary endpoints in a real-world population. We compared progression-free survival (PFS) and overall survival (OS) measured in the CheckMate-017 and CheckMate-057 clinical trials with the same endpoints (OS, PFS) of the patients cured in our hospital.

Methods: With the help of our hospital medical informatical system the anamnesis of 83 patients (50 men, 33 women) receiving nivolumab was reviewed retrospectively. The data were statistically analyzed; PFS, OS and survival curves were determined using SPSS software.

Results: In ADC (43 patients, median age 62 years) the median OS was 9.8 months, the one-year OS rate was 37.2%, the median PFS was 2.9 months, the one-year PFS rate was 11.6%. In SCC (40 patients, median age 63.5 years) the median OS was 13.3 months, the one-year OS rate was 55.0%, the median PFS was 6.2 months, the one-year PFS rate was 30.0%. In the case of ADC, the effectiveness results measured in our institution are poorer, while in SCC are more beneficial, than the efficacy results measured in the clinical trials.

Conclusion: Based on these results, the gap between efficacy demonstrated in clinical trials and effectiveness experienced in real-world studies can be quantified. Effectiveness data registered in our institution can be regarded as a suitable base for the development of outcome-based financial models. With such data analyses we can capture the real value of nivolumab in NSCLC therapy in Hungary and create an outcome-based financing scheme.

The development of a semi-solid formulation containing cinnamon essential oil as a hand-sanitizer preparation

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Background: Pharmacy practice includes traditional and extemporaneous 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.

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

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; 60±5% relative humidity. The preparations were monitored, and few units of the reference material were taken at 1, 3 and 6 month intervals. During the stability testing process the following experiments and tests were conducted according to the Hungarian and European Pharmacopoeias: Dropping point and freezing point measurements, extensometric test, microscopic examination, pH measurements of the aqueous 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 physicochemical parameters. Based on the study, we can recommend a good manufacturing practice, expiry date, packaging material and storage conditions regarding the chosen formulation.

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

References: 1 WHO Expert Committee on Specifications for Pharmaceutical Preparations – WHO Technical Report Series, No. 863 – Thirty-fourth Report; 2 Falconer, J.R. & Steadman, K.J. Aust Prescr 2017;40,5-8.

Dr. (Hermányi) Sztankay Aba from Debrecen as a pharmacist he became a private university teacher

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Family roots: The Sztankay family comes from Croatia and their original name was Ztanechich. The family can be traced back to János Ztanechich, who was the secretary of the Transylvanian prince

István Báthori. Nobility was given to the family by the Transylvanian prince Zsigmond Báthori on May 26, 1596. During the religious upheavals, a member of the family converted to the Lutheran faith and therefore he fled to Gömör County. A pharmacist and landowner from Selmecbánya, Ferenc Sztankay (April 19, 1835 – May 29, 1910) was descended from this family branch. He married Abraham Rosalia on October 18, 1864 in Verespatak. Eleven children were born from the marriage, but most of them did not reach adulthood. The family moved from Verespatak to Selmecbánya in 1873, where Ferenc first became the owner of a pharmacy and then a landowner, thus ensuring his family welfare. Three children were born in Verespatak: Gyula Aba (March 27, 1868 – January 21, 1936) – the protagonist of our story – humanities scientist, pharmacist and university private teacher, Béla Farkas (1869 – 1955) graduated engineer, director of the Royal Industrial School, first in Gölniczbánya and then in Debrecen, and Margit (1870 -?). Sztankay Aba married Sára Zsilkay in 1895. From their marriage three daughters were born: Klára (1895-1920); Sára, who died of pneumonia in 1936, and Dóra, who married Major General Lajos Burget and left the country in 1947. One daughter was born from their marriage, Dorothea (Thea) (June 2, 1926 – November 29, 2016), she moved to the United States where she married and had two children.

The most outstanding successes of his work:

I. *He was only 16 years old when he published his dissertations on the history of pharmacy in the weekly "Aesculap", with which he also helped the development of the terminologie of pharmacy.*
II. *From 1886 onwards, his writings were published in Hungarian and German, among which it is worth mentioning e.g. the "Handbook of Urine Tests, for practicing pharmacists, physicians and those dealing with similar chemical tests", or "Commentary in Section II of the Hungarian Pharmacopoeia" or "the correctness of the information provided in the appendix of the Hungarian Pharmacopoeia on the content of Tokaj wine extract".*
III. *In the laboratory of the pharmacy "Salvator" in Bát, he produced an intestinal disinfectant and anti-diarrhoea drugs called "Tanninum albuminatum keratinatum", which was known to the public as his fancy name "Hontin". As he could not find a domestic manufacturer, he was forced to sell it to an Austrian company, through which the product spread throughout Europe. (For posterity, he continued to live under the name "Albumen tannicim" – PhHg VII.)*
IV. *In the Hungarian Pharmacopoeia II, a preparation containing theobromine, called "Diureticum", was official. Because theobromine is poorly soluble in water, Sztankay experimented with a more beneficial compound that resulted in "Theobromino natriosalycilicum" and then "Anisotheobromine".*
V. *In 1900, Professor Vámossy discovered the laxative effect of phenolphthalein. In his long experiments, Sztankay found that the drug is more soluble in water in its amorphous state and thus more effective than in crystalline form. Stankay formed amorphous phenolphthalein using NaOH. He named this compound "Eulaxans". The product containing phenolphthalein with Na_2CO_3 was named "Perrectal", suggesting that it is an excellent laxative when administered rectally and can be used even in animals.*

Risk assessment in preparation of magistral medicines

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Background: The Committee of Ministers Resolution CM/ResAp (2011)1 on quality and safety assurance requirements for medicinal products prepared in pharmacies for the special needs of patients. It serves to assess the potential risk factors for the new medicinal products which is prepared in pharmacies. This resolution is a recommendation and does not give a specified method for a fully objective risk analysis; we have begun to develop a new, more comprehensive risk analysis system.
Aims: To develop a more detailed methodology which can help to identify, analyze, and evaluate potential risks in preparing, quality and stability of products prepared in pharmacies and determine how to minimize chemical exposure for the pharmacy staff's health, and how to ensure the safety medication of patients.
Methods: Risk analysis based on a developed table with objective choices. Using points system, the percentage of objectively qualified risk that value can be evaluated in textual form, thus the nature of the risk can be determined.
Results: The developed mathematical-based method quantifies the risk, and the value expressed as a percentage which gives the degree of risk. The pharmacist considering the risk and decide to prepare a high-risk preparation, or minimize the risk by applying appropriate precautions.
Conclusions: There are different sources of risk including the events, causes and consequences during the preparations of magistral medicines. The elaborate set of criteria seeks to fully identify potential risk factors. The severity assessment of the risk gives information to minimize the risk.

Personalized intranasal device development

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Background: Air pollution is a global health threat and causes millions of human deaths annually. The late onset of respiratory diseases in children and adults due to prenatal or perinatal exposure to air pollutants is emerging as a critical concern in human health. Globally, seven million deaths were attributable to the joint effects of household and ambient air pollution. Subjects with chronic respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma are especially vulnerable to the detrimental effects of air pollutants. Air pollution can induce the acute exacerbation of COPD and onset of asthma, increase the respiratory morbidity and mortality. The health effects of air pollution depend on the components and sources of pollutants, which varied with countries, seasons, and times.
Aims: The objective of this research was to develop personalized nasal filters by 3D fused deposition modeling technique. The design had been performed by 3D imaging technique and prototypes had been manufactured at the department by FDM 3D printer. As the part of the development our aim was to evaluate the physical properties of the formulated devices as well. According to the research plan the final output of the project is two products; a simple nasal filter for everyday use and a medical device with different application possibilities.
Methods: Main tasks of research are; state-of-the-art literature research. 3D modeling, design and development. Application of pharmaceutical technology rules at the formulation stages. Test, validation and calibration of the developed models and control procedure according to pharmaceutical standards. In vitro biocompatibility measurements.
Results: First class devices are 2 ways multi Cores nasal equipments intended to protect users from harmful allergens in the growingly polluted environment, their designs in theory were meticulous, but still lacking sufficient testing. There are 5 designs until now: Mk1, Mk2, Mk3, Mk4, MkV; each was an improvement from the last, each was inspired from the previous model, but they all carry their merits and their disadvantages. Emergency Nasal Filters are 3D printed functional nasal filters with several possible fuctions that patients can rely on whenever and whatever situation.
Conclusion: We can conlude that 3D printing tehnique is the most suitable procedure for our formulation. Our development, combined with biocompatibility measurements ensure innovative product and safe application as well.

Development of magistral preparation containing omeprazole

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Background: Many drugs frequently used in neonatology are not available in suitable dosage forms, in such cases compounded medicines have to be prepared. In addition, it is often the case the absence of an active pharmaceutical ingredient (API), therefore authorized medicines have to be used, as a source of it. For the accurate dosage and reproducibility, the divided or diluted omeprazole content pellets are not adequate formulations, thus a different technological solution is needed.
Aims: The objectives of the project was the development of omeprazole containing dosage forms for pediatrics, refer to the relevant international guidance and to other guidelines.
Methods: Prepare and compare the suspensions from Losec® and Ludea® capsules. Pellets were dispersed in an 8.4 % sodium bicarbonate solution. The compounded suspensions were prepared differently by stirring, grinding and shaking methods, and stored at 2-8 °C. The aspects of the examinations were the resuspendability, pH, dose uniformity and microbiological purity.
Results: Based on the results, we selected the most appropriate formulation and preparation method for shelf life.
Conclusions: Further develop to the experience of the literature, a safe and cost effective omeprazole suspension can be prepared. This dosage form can reduce the lack of available medicines in the field of pediatrics.

Variability in response to antidepressant therapy: a pharmacogenetic approach

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Background: The process of the first pass metabolism is accomplished by several number of enzymes. In numerous pharmacogenetic researches the Cytochrome P450 System, consisting of approximately

60 genes, which encode hepatic heme-proteins was investigated. Since, these enzymes play key role in the drug metabolism, the different variants can cause changes in their function that can lead to altered metabolism rate by affecting pharmacokinetic and pharmacodynamic properties. The metabolism rate can be categorized as poor (PM), intermediate (IM), extensive (EM) and ultrarapid (UM).

Aims: The aim was to obtain a comprehensive knowledge about the latest studies investigated this topic.

Methods: I have reviewed some of the latest articles observing the relation between responses to antidepressant treatment and variants in CYP450 family and extracted the most relevant result.

Results: The most studied genes and their variants that have impact on the therapeutic response are CYP2B6, CYP2D6 and CYP2C19 related to the metabolism of paroxetine, escitalopram, citalopram, mirtazapine, desvenlafaxine and sertraline. Paroxetine and mirtazapine showed decreased efficacy in case of the increased function (EM status) of the CYP2D6 enzyme and since the metabolism of sertraline is also mediated by CYP2B6 and CYP2D6, polymorphisms of these genes may also affect the drug plasma concentration during therapy. The altered metabolism of desvenlafaxine caused by polymorphism of CYP2D6 showed lower risk than the other observed antidepressant. Escitalopram and citalopram were more effective in patients with IM status of CYP2D6 and CYP2C19 enzymes and slower CYP2C19 metabolizers (PM status) experienced side effects.

Conclusion: The individual drug therapy could be a great step in the development of the antidepressant therapies, allowing increased therapeutic efficacy and decreased risk of side-effects. To obtain this, the investigation of the responses to antidepressant therapy related to the pharmacogenetic background of an individual is indispensable.

Preformulation studies of ciprofloxacin-loaded polymer-based electrospun nanofibers

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Background: Polymer-based electrospun nanofibers are considered as a novel nanocarriers which have numerous advantages such as wide variety of polymers and active pharmaceutical ingredient (API), large surface area and adjustable diameter. Nanofibers mostly prepared by electrospinning process. Incorporation into nanofibers can improve the physico-chemical properties of the API important pharmaceutical technological aspect. Ciprofloxacin (CIP) is a worldwide used fluoroquinolone antibiotic for local and systemic therapy. CIP is a BCS Class II drug indicated by its solubility and permeability.

Aims: Therefore, the aim of the study was to produce and investigate various polyvinyl-pyrrolidone (PVP) based nanofibers and to find the optimal composition and the appropriate technological parameters to improve the physico-chemical properties of CIP. As a result, the in vitro dissolution rate could be therefore increased.

Methods: Nanofibers in different combination of ingredients (1:0, 1:1, 1:2, 1:3 PVP:CIP) and also nanofibers produced by different flow rate (0,5; 1; 1,5; 2; 3; 4 ml/h) was made. To compare and characterize the samples the micrometric (SEM) and the structural (DSC, XRPD) properties were investigated. The fiber-diameter and in vitro dissolution profiles were also examined.

Results: Conceivably, the nanofiber sample contained 1:1 PVP:CIP and prepared by 2 ml/h flow rate had the best properties. The dissolution rate of ciprofloxacin could increase by formulation of amorphous solid dispersion.

Conclusion: According to this electrospun nanofibers would increase the dissolution of ciprofloxacin. The development of a new pharmaceutical dosage-form with better physico-chemical properties is possible to start after further investigations.

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Application of machine learning in the identification of oral medicines: a new tool to combat against falsified medicines and increase medication safety

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Background: There has been a tremendous focus on falsified medicines in the recent years with more and more regulations have entering into force globally, and in Europe as well. Although, the chance of falsified medicines entering into the regulated drug supply chain is considered to be low in developed countries, unregulated illicit internet sale of medications is an international issue. Illicit internet pharmacies are flourishing and we have limited tools to combat against them and illegally purchased medi-

cines pose a significant medication safety and patient safety risk. The traditional analytical methods have their limitations (time consuming, costly and large sample need). Our previous literature reviews and market searches proved, that currently there is not any mobile software with image recognition that meets this emerging public health need.

Aims: Our aim is to develop a Software as a Service (SaaS) cloud native solution that is able to identify efficiently oral dosage forms.

Methods: During our work we specified a protocol to photograph medicines. We have taken 50.000 photos of 100 medications as follows: 75 photos were taken from the front of the secondary packaging (medicine box), 75 photos from the back. 50 photos were taken of the front of the primary packaging (blister), 50 photos of the back. Further, a total of 250 photos were taken of the drug (tablet, capsule, etc.) itself. We used the Tensorflow Machine Learning library to implement our algorithm. The core of the algorithm is a pre-trained visual convolutional neural network, that was fine-tuned to be able to recognize and classify different type of medicines and medicine boxes. During recognition, the network outputs the most probable medicine candidates with their probability-like measure. Visualization of the performance of an algorithm is evaluated on a confusion matrix and Type I and Type II errors

Results: In our experiments the trained neural network achieved ~90% top-1 accuracy (most probable candidate) on a single image. The results show, that the color and the shape factor have the largest contribution to the confusion between the top-k candidates. In most cases, this accuracy can be improved with aggregating multiple different images of the medicine.

Conclusion: Future application of such methodology can be used in forensics, for public use, to prevent medication error and recognizing drug interactions.

Formulation and studies of the sunscreen's biocosmetics

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Background: The benefits of biocosmetics are based on natural ingredients that help maintain the skin's natural state. Some preparation has sunscreen effect when its component or combination of components provides adequate protection against sun rays.

Aims: The aim of this experimental work is the formulation and studies of the cosmetic preparations obtained with extracts of four medicinal plants selected from the spontaneous flora of Transylvania: *Vaccinium myrtillus* (fructus), *Hippophae rhamnoides* (fructus), *Rubus caesius* (fructus), *Calendula officinalis* (flos).

Methods: The lyophilized plant extracts were embedded individually, and in one case blueberry with marigold together, in a Carbopol-based gel and in a o/w cream. The total polyphenol and the total flavonoid content were determined by spectrophotometric method from plants ethanolic extracts and from lyophilisated products. Also with spectrophotometric method were determined the antioxidant capacity by ABTS and DPPH method. The consistency of the gels and creams were determined by rotary viscometer, extensometric and penetrometric methods. The amount of polyphenol dissolved in the gels was determined by in vitro dissolution method.

Results: The total polyphenol and the total flavonoid content from plant ethanolic extracts and lyophilized products were with the same or higher (243mg/100g lyophilised product from Rubi caesii fructus) values with data from literature. The highest concentration of polyphenols and flavonoids were determined from the blackberry extracts. The combination of the two extracts – blackberry and marigold – proved to be effective in vitro dissolution studies, in the meantime the highest polyphenol content was measured from these gels, too. The creams have a pseudoplastic flow (average of creams viscosity: 25Pas and gels viscosity: 15Pas) and the extensometric and penetrometric measurements showed a higher consistency against the gels.

Conclusion: We can conclude that the physicochemical properties, dissolution and the sunscreen character of the creams and gels with antioxidant properties related with the polyphenol content, it was more advantageous in combination of blackberry and marigold lyophillized extracts in gels than gels obtained individually from by one extract.

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Survey of drug shortages in Hungary

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Background: Drug shortages have become a global public health threat in the recent years and healthcare systems and professionals are struggling to dispense the ordered medications to patients in the hospitals and in the community pharmacies as well.

Aims: As there are limited date regarding drug shortage prevalence and affected therapeutic categories in Hungary, our aim was to assess the characteristics and collect evidence regarding this phenomenon from Hungarian pharmacists.
Methods: With an extensive literature search in 2019 April, we identified 53 surveys. After their review, we developed our Hungarian version with 45 questions categorized in 5 main sections: 1. Pharmacy data and demographics; 2. Prevalence and background; 3. The management of drug shortages; 4. Information sources; 5. Consequences of drug shortages. Data was collected between 15. May and 30. June 2019 with an online survey among pharmacists.
Results: 42 hospital and 49 community pharmacists completed the survey. 70 women and 21 men, mainly between the ages 25-40 years, from various type of pharmacies. 52.4% of the hospital pharmacists and 97.9% of community pharmacists experienced drug shortages more than 10 times in the last 6 months. The top ATC groups were the followings in hospital settings: B – Blood and blood forming organs (52.4%); C – Cardiovascular system (50%); L – Antineoplastic and immunomodulating agents (47.6%); J – Antiinfectives for systemic use (38.1%); N – Nervous system (38.1%) APIs such as immunoglobulins, digoxin, phytomenadione, amoxicillin/clavulanic acid. The main affected therapeutic areas in the community pharmacies were the C – Cardiovascular system (89.6%), N – Nervous system (43.8%) and A – Alimentary tract and metabolism (31.3%) including API bupropion, acarbose, metoclopramide and tramadol. Original and generic drugs, parenteral and oral dosage forms were equally affected at the time of our study. The main reasons highlighted by pharmacists were manufacturing problems, tendering processes, and serialization.
Conclusion: Drug shortages affect the Hungarian pharmacists and patient care as well, with similar tendencies that can be seen globally. We should collect and analyze further data to find possible long-term solutions to manage drug supply problems in various therapeutic areas.

Risk based safety mapping of online pharmaceutical market: A case of ophthalmic preparations

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Background: The growing number of illicit internet pharmacies is a global phenomenon, however the size of the online pharmaceutical market is still unknown and quality of products is of great concern. Descriptive data of this dubious market channel are derived from studies analyzing the online availability of different medications purchased over the internet and their methodology is quite heterogeneous.
Aims: Our aim was to develop a comprehensive and also specific risk evaluation method to select ophthalmic medications with high patient safety risk from the online pharmaceutical market.
Methods: Ten eye drops were selected based upon their sales in every day practice in a community pharmacy in Hungary. As there is no specific risk assessment tool for the risk evaluation of the online pharmaceutical distribution channel, a new tool was developed based upon the two quality and safety standard resolutions in pharmaceutical practice published by the European Directorate for the Quality of Medicines.
Results: We developed 6 criteria for the risk assessment of eye drops: I. General pharmaceutical risks, II. Risk originated from the pharmacological property of the active ingredient, III. Risk associated with application, IV. Risk of microbiological contamination, V. Risk from the limited access to the product, VI. Risk related to potential misuse. The above six criteria were integrated in a comprehensive weighted risk scoring system (maximum 30 points). The probability of purchasing the product from the internet was also assessed based on the number of relevant links in search engine results (0-20 links) and the price of the products (<25 USD; 25-50 USD; >25 USD). The product got 1 point if it was sold on 20 or more websites, and 1 point if the price was less than 25 USD. Based on the above criteria timolol/dorzolamide combination products had the highest overall patient safety risk in the risk assessment matrix with 20 points in the patient safety consequences (severity) and 2 points in the total probability score (likelihood).
Conclusion: Currently, there is no standardized methodology to select specific pharmaceutical products with high patient safety risk for analyzing internet pharmaceutical market and as the test purchase cannot be performed for all of the medicines available, we developed a method that may help in designing and focus similar research and can also be used in case of targeted joint actions against medicine counterfeiting (e.g.: Operation Pangea).

Off-label solutions to create magistral medicines in our paediatric clinic

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Background: In the every-day practice of pharmacy,

particularly in paediatrics, we often confront the challenge of the lack of appropriate dosage form of a required agent. We strive to fill this gap in the therapy with magistral preparations. If the positive list of the National Institute of Pharmacy and Nutrition miss the necessary agents, the required dosage form is prepared from pharmaceutical specialties, even if it is off label.

Aim: It is high importance to us to create safe and efficient as well as easily applicable and comfortable therapeutical solutions for our inpatients with different severe conditions.

Methods: We realise the respective innovative ideas in a close collaboration with our specialist physicians. Taking into account the international practice, we strive to find solutions that resemble some medication registered in an other country, possibly in the USA. If this is not possible, we construct the necessary formulae based on our professional knowledge, the medical literature, and guidelines.

Results: Replacing the clysters registered and distributed in Hungary to treat epileptic seizures promised and delivered great success for both children and relatives. We have managed to largely replace the rectally administered solutions with nasally via-MAD applied midazolam for our patients suffering from epilepsy, therewith achieving a more practical treatment of acute seizures.

We also prepare budesonide suspensions to successfully treat the pharyngealis and esophagealis erosions of the affected patients with Crohn's disease.

Children suffering from SMA who received gene therapy – Zolgensma – are administered with prednisolone and famotidine following the US protocol.

Conclusion: In order to provide our patients and physicians with medicines that offer the most optimal therapy, one needs to be open to off-label magistral solutions. Construction of the appropriate medication is within the competence of the pharmacist of high, which can effeciently contribute to the successful medical attendance of our patients

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Application of nanotechnology in formulation of tioconazole and tea tree essential oil for onychomycosis topical treatment

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Background: The topical therapy of widespread onychomycosis is a long process (10-12 months) and has a low cure rate. 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 a broad antifungal spectrum and it can show synergism with essential oils (EOs). Tioconazole (TO) and tea tree EO (TT) have been chosen for this research. Pickering emulsions (PEs) are stabilized with nanoparticles instead of surfactants, 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.

Aims: Our aim was to prepare silica nanoparticle stabilized PE of TO and TT, which are suitable for onychomycosis topical treatment.

Methods: Because of the lipophilic character of TO, it can be dissolved in TT, and their solution can be used as oil phase for PE preparation. Surface modified Stöber silica nanoparticles (SNPs) were prepared, characterized and used as stabilizing agent of PEs. We have tested the ratio of oil phase to SNP and the size of SNP on the resulting droplet size and stability of PEs, which were determined with DLS measurements. We examined the diffusion properties of PEs through the nail plate and nail matrix model membrane and investigated their antifungal activity against *Candida albicans* and *Trichophyton rubrum*, which species are mainly responsible for fungal nail infections.

Results: The droplet size of emulsion has a correlation with the SNP to oil ratio and with particle size of SNP. The results of diffusion study show, that the droplet size of PEs and particle size of SNPs influence the diffusion properties of PE through the nail plate and nail matrix model membranes. Microbiological examinations show a synergistic effect between TO and TT, furthermore, PE forms show the most effective antifungal activity against *C. albicans* and *T. rubrum* compared with conventional emulsions or ethanolic solution forms.

Conclusion: Our results show, that with PE form selective drug release can be achieved because TO diffuses only through the nail plate where it can act against fungal infection, what makes this drug form applicable in the topical treatment of onychomycosis.

A jövő kötelez

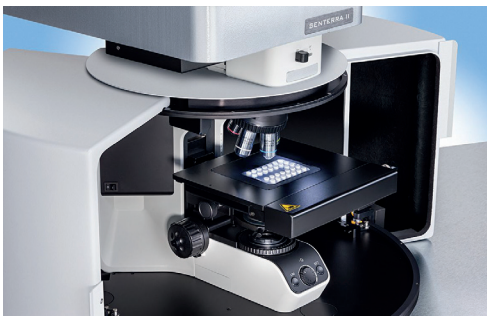
Debrecen, 2020. szeptember 10-12.

Raman mikroszkópia és képalkotás előnyei a gyógyszeripari QC és a K & F területén

A gyógyszerekkel kapcsolatos legkisebb problémák veszélyes és legrosszabb esetekben akár halálos forgatókönyvekhez is vezethetnek. Ezért ezeknek a gyógyszereknek az elemzésekor nincs helye a kompromisszumnak. A szabályozott környezetben előforduló gyártási hibákat alaposan ellenőrizni kell, és a gyógyszerek minőség-ellenőrzésének minden tekintetben pontosnak és kifinomultnak kell lennie.

Mi lehet a legjobb módszer egy tabletta összetételének vagy az API-k eloszlásának ellenőrzésére? Hogyan lehet megfelelően pontosan elemezni az ismeretlen alkotóelemeket vagy szennyeződéseket, és meg lehet-e védeni magunkat a versenytársak jogsértései ellen?

A Raman mikroszkópia és képalkotás egyértelmű választ ad ezekre a kérdésekre. Használható gyógyszerek szilárd adagolási formákban, például tablettákban és granulátumokban történő tesztelésére, de képes megkülönböztetni a polimorf anyagokat is és lehetőséget kínál még nem invazív elemzésre, beleértve a mélységi profilozást is. A Raman-mikroszkópia nagy mennyiségű információt szolgáltat molekuláris szinten tiszta polimorf, kristályos és amorf szilárd anyagokra, valamint folyékony készítményekre, spray-kre és aeroszol termékekre.



A molekuláris szerkezet vagy morfológia változásainak kimutatása és a tartalom egyenletes eloszlásának, homogenitásának és részecskeméretének kiértékelése mind lehetséges Raman-mikroszkópiával. Ennek a nagy teljesítményű spektroszkópiai módszernek a szabályozott környezetben történő használatához ugyanolyan erős és validált eszközre van szükség és a Bruker SENTERRA II Raman képalkotó mikroszkóp készen áll ezeknek a feladatoknak az elvégzésére.

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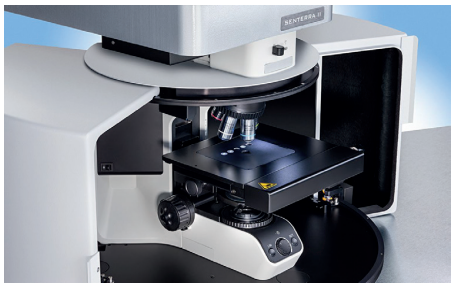

Gyorsan és szoftveresen váltható több lézeres gerjesztés és minimalizált fluoreszcencia az opcionális 1064 nm-es gerjesztéssel teszi teljessé a SENTERRA II tulajdonságait. A SENTERRA II magában foglalja a teljesen automatizált műszervizsgálati eljárásokat is, az USP 1120, Ph. Eur., 2.2.48, ASTM E1840 és E2529-06 szabványoknak megfelelően. Ezenkívül teljes mértékben megfelel a GMP, a cGMP, a GLP és a 21 CFR Part 11 követelményeinek. Igény esetén rendszer-validálási kézikönyv áll rendelkezésre a DQ/IQ/OQ/ PQ és a validálási szolgáltatások dokumentálása számára.

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