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Smarter Medicine – Better Care

International Conference on Pharmaceutical Sciences

September 24–26, 2026
Siófok – Hungary

Book of Abstracts

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Contents

Plenary lectures S5

Oral presentations S10

Poster presentations. S46



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PLENARY LECTURES

(The abstracts are arranged in alphabetical order.)

ADVANCED DRUG DELIVERY SYSTEMS FOR BRAIN REPAIR AND NEURORESTORATION

Maria Blanco Prieto
Past President of EUFEPS, University of Navarra, Navarra, Spain

Parkinson's disease (PD) remains an incurable neurodegenerative disorder, and current treatments are largely limited to symptomatic relief without modifying disease progression. Neurotrophic factors, particularly glial cell line-derived neurotrophic factor (GDNF), have shown strong potential to protect and restore dopaminergic neurons, but their clinical translation has been hampered by major challenges related to delivery, dosing, and safety.

This lecture will present the development and preclinical validation of advanced drug delivery systems based on biodegradable PLGA microspheres and brain-compatible hydrogels for the sustained and localized delivery of GDNF to the brain. We will review results obtained in rodent and non-human primate models of Parkinson's disease, demonstrating long-term functional recovery, restoration of dopaminergic innervation, and an excellent safety profile. In addition, novel tissue engineering strategies combining GDNF delivery with nanoreinforced hydrogels and stem cells will be discussed as a multi-regenerative approach for brain repair.

Overall, these findings support advanced delivery systems as a promising and clinically relevant strategy to enable neurorestorative therapies for Parkinson's disease and other neurodegenerative disorders.

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NANOMEDICINE FOR RNA DELIVERY: TOWARDS PRECISION MEDICINE?

Giuseppe De Rosa
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RNA-based medicine represents a new key tool for new and efficient therapeutic strategies. Altered protein expression can be restored by using messenger RNA (mRNA), while non-coding RNA oligonucleotides, e.g. small interfering RNA (siRNA) and micro-RNA (miRNA) can be used to restore altered cell process.

The poor biopharmaceutical profile of RNA therapeutics requires the use of delivery systems. In this context, the approval of Onpattro® and following unquestionable success of the two RNA-based vaccines Comirnaty® and Spikevax® consecrated the lipid nanoparticles (LNP) as the leading delivery system for translation of RNA-therapeutics in clinical practice.

LNP can be successfully used for the delivery of non-coding RNA, e.g. miRNA, for the treatment of different form of cancer. Targeted LNP encapsulating miRNAs have been also proposed [1]. LNP encapsulating miRNA have also been used to overcome chemoresistance occurring in the case of immunotherapy [2,3]. Recently, the ability to use LNP to deliver therapeutic miRNA in the CNS to treat brain metastasis has also been demonstrated [4]. On the other hand, targeted LNP encapsulating miRNAs have also been proposed to reduce the brain damage following ischemia [5].

Despite the success of lipid nanoparticles (LNP), some issues still need to be addressed, among them the poor physical stability of RNA-encapsulating LNP that requires low temperatures for storage and transport. Our research group developed a novel nanotechnology approach named lipid self-assembling nanoparticle (SANP) as alternative platform for RNA delivery. Lipid SANP formulations, previously developed

by our group have shown remarkable biocompatibility, high RNA encapsulation efficiency, and enhanced intracellular release. Furthermore, SANP have been designed to be prepared at room temperature immediately before use by simple mixing of three components, namely, calcium/phosphate dispersion, RNA and cationic liposomes. By using this approach, the RNA can be stored and used in a lyophilized form, which ensures greater stability against degradation compared to freezing. This approach could also be used for personalized medicine, thus developing into the hospital personalized formulations encapsulating noncoding RNA selected for the specific patient.

SANPs developed for the delivery miRNA [6] or siRNA [7] in the treatment of different tumors have been proposed. SANPs encapsulating mRNA have also been successfully proposed for vaccination purpose [8]. Further development includes the inclusion of "bioactive" components into the SANP able to prevent neuron damage following oxidative stress, thus making this technology of interest for the treatment of neurodegenerative diseases [9,10].

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DIGITALIZATION IN THE PHARMA INDUSTRY: OPPORTUNITY OR CHALLENGE?

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Head of Digitalization, Industrial Operation Euroapi, Budapest, Hungary

Digitalization is transforming pharmaceutical manufacturing and operations, redefining how companies design, monitor, and optimize their industrial processes.

In this plenary presentation, demostrative examples are planned to be shown how digital tools - such as data analytics, digital twins, end to end planning and follow up, AI based tools - are reshaping the daily realities of pharma production. The talk highlights the tangible opportunities these technologies create: increased operational efficiency, enhanced process robustness, improved compliance, and more agile decisionmaking across the value chain. At the same time, it addresses the challenges that accompany this shift, including data governance, cybersecurity risks, workforce upskilling, and the complexities of modernizing legacy infrastructures.

Through practical industrial examples and lessons learned from implementation, the presentation offers a balanced perspective on how organizations can navigate digitalization strategically and sustainably. Participants are invited to reflect on how the industry can convert operational complexity into longterm value and ensure that digital transformation strengthens both manufacturing performance and patient trust.

DEVELOPMENT OF A HEALTH INDUSTRY INNOVATION ECOSYSTEM THROUGH UNIVERSITY AND CORPORATE COLLABORATION

Balázs Lendvai
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Richter Gedeon Plc., Budapest, Hungary

Europe's innovation performance is hindered by three mutually reinforcing barriers: misaligned incentives between academia and industry, inflexible public funding mechanisms and fragmented collaboration structures. When establishing the Richter Innovation Ecosystem our endeavor was to demonstrate a scalable alternative for academy-industry relationship by prioritizing structure before funding. Central to this approach is early alignment on a shared value proposition focused on unmet medical needs, ensuring that both scientific outputs and industrial translational results are recognized as success metrics. Trust-building mechanisms—including open innovation principles, clear IP rules, and unrestricted publication rights—further enable productive exchange. A multilateral governance framework defines roles, decision rights, and agile operating practices that accommodate scientific pivots even within rigid grant schemes. Supported by coordinated workshops and strong core-facility infrastructure, the ecosystem tracks collaboration intensity, translational progress and network growth as leading indicators. Initial outcomes show that structured, trust-based ecosystems can open new pathways to competitiveness if paired with flexible governance models.

NUCLEOSIDE-MODIFIED MRNA: THE PAST, PRESENT AND FUTURE

Norbert Pardi
Department of Microbiology of the Perelman School of Medicine, Pennsylvania, USA

The real-life success of nucleoside-modified mRNA vaccines during the COVID-19 pandemic validated the viability of this groundbreaking platform technology. Development of mRNA vaccines was not an overnight success, but multi-year development was necessary to create this novel type of medicine. Dr. Pardi will summarize the most critical findings that led to the birth of mRNA vaccines/medicines and will tell about the current standing of the field as well as outlook for the future.

SILICONE-BASED TRANSDERMAL PATCH DEVELOPMENT: TRANSLATING ACADEMIC INNOVATION INTO PRECLINICAL REALITY

Erika Pintér
Pharmacology and Pharmacotherapy, Faculty of Medicine, University of Pecs, Pécs, Hungary

Introduction: Persistent nociceptive and neuropathic pain often remain inadequately controlled by currently available pharmacological treatments, highlighting the need for safe and effective non-opioid analgesic strategies. We previously demonstrated that a novel silicone-based transdermal therapeutic system (TTS) co-formulated with low-dose capsaicin and diclofenac provides prolonged analgesic efficacy in both acute and chronic pain models (Göntér et al., 2025). Here, we further evaluated its multimodal analgesic efficacy and translational potential in post-incisional pain, carrageenan-induced inflammation, partial sciatic nerve ligation (PSNL), and monosodium iodoacetate (MIA)-induced osteoarthritis.

Materials and Methods: Drug release was assessed by Franz diffusion and flow-through cell assays, demonstrating near zero-order kinetics and enhanced mutual permeation. Analgesic efficacy was investigated using thermal hyperalgesia and dynamic plantar aesthesiometry (DPA) in acute post-incisional and carrageenan models at baseline, after induction, and 2.5 and 6 h after TTS application (capsaicin: 0.39 mg/cm^2; diclofenac: 0.39 mg/cm^2; combination: 0.38 + 0.38 mg/cm^2; placebo). Mechanical allodynia was assessed in PSNL rats on days 7, 14, and 21, and in MIA-induced osteoarthritis on days 7 and 15 together with dynamic weight bearing and knee joint diameter measurements.

Results: The dual-agent patch ensured continuous drug delivery with near zero-order release. In acute models, the combination significantly reduced thermal and mechanical hypersensitivity at both 2.5 and 6 h, outperforming monotherapies. In PSNL animals, combined and capsaicin-only formulations restored withdrawal thresholds to near-baseline values. In MIA-induced osteoarthritis, the dual patch reduced pain-related behaviour, improved weight distribution, and attenuat-

ed joint swelling compared with single-agent treatments.

Conclusions: The silicone-based capsaicin–diclofenac TTS provides prolonged analgesia through controlled drug release and shows efficacy across inflammatory, post-surgical, neuropathic, and degenerative pain models. These findings support its potential as a novel non-opioid treatment for persistent pain. The technology is currently progressing through preclinical development. A dedicated startup company was established to advance clinical translation and received private funding in 2025 to support preparation of the preclinical regulatory dossier.

Patent pending: P2200237 (27 June 2022); PCT/HU2023/050042 (27 June 2023); US 63/615,177 (27 December 2023).

Funding: TKP2021-EGA-13; Proof of Concept Grant, University of Pécs, 2024–2025; additional private investment (2025).

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SEEING WITH MANY EYES: A SHARED VISION FOR MEDICATION STEWARDSHIP

András Süle
European Association of Hospital Pharmacists, Belgium; Faculty of Pharmacy, University of Pécs; Péterfy Hospital and Outpatient Clinic, Budapest, Hungary

Medication stewardship is increasingly recognized as a unifying framework for optimized medicines use while protecting the sustainability and resilience of health systems. Building on recent conceptual work and practical experience from diverse stewardship programs, this keynote will explore how clinical pharmacy services, strategic workforce development and context-sensitive use of automation can together underpin a future-ready approach to medication use in BBBB countries and beyond.

Clinical pharmacy services, acting as a hub for safe medicines use policies, highlight the central role of pharmacists in translating stewardship principles into day-to-day practice across high-risk domains such as antimicrobials, anticoagulation, opioids and complex polypharmacy. Evidence from hospital and specialty settings will be used to illustrate how integrated clinical pharmacy services can reduce drug-related problems, improve patient outcomes and generate measurable cost savings when embedded in multidisciplinary teams. This section will contrast traditional product-focused models of pharmacy with outcome-oriented stewardship models that emphasize appropriateness, individualization and shared accountability for therapeutic decisions.

Scalability of such services require resilient workforce planning and educational readiness. Against a backdrop of ageing populations and healthcare workforce shortages in Europe, health systems face growing difficulty in maintaining sufficient numbers of appropriately skilled pharmacists and other professionals. The keynote will discuss competency profiles for clinical pharmacy and medication stewardship, the importance of structured postgraduate training and advanced practice pathways, and the value of interprofessional education in enabling pharmacists to contribute effectively to diagnostic, therapeutic and medication-related decision-making.

As a third aspect, the role of automation, robotics and machine learning techniques will be discussed as potential force multipliers for, rather than replacements of, professional judgement in medication use policies. Examples from pharmacy automation will be used to argue for prioritizing mature areas such as storage and inventory management, which can improve safety, efficiency and shortage management, over narrow, one-size-fits-all unit-dose solutions. Emphasis will be placed on careful process analysis, locally appropriate implementation and governance arrangements that ensure transparency, validation and accountability for ML-enabled decision support.

Finally, the keynote will connect bedside and frontline patient care stewardship efforts with upstream determinants such as procurement practices, tendering models and the growing challenge of medicine shortages across Europe and worldwide. Hospital pharmacists' contributions to risk-aware tender design, multi-criteria decision-making and shortage mitigation strategies will be highlighted, alongside the need for stronger data, communication and collaboration across supply chains to protect continuity of care.

CYTOPROTECTIVE MECHANISMS OF RESVERATROL DERIVATIVES AND THEIR STRUCTURE-ACTIVITY RELATIONSHIPS

Tamás Tábi, Kamilla Varga, Alexandra Paszternák, Noémi Sikur, Éva Szökő
Department of Pharmacodynamics, Semmelweis University, Budapest, Hungary

Resveratrol is a naturally occurring stilbene derivative with a broad range of pharmacological activities. It is found in various plant sources, including red wine, and has been proposed to contribute to the so-called French Paradox through its cytoprotective effects. However, resveratrol undergoes extensive metabolic transformation, resulting in low oral bioavailability and limited therapeutic potential. In our previous studies, we demonstrated its cytoprotective effects resembling to preconditioning process as resveratrol induced mild mitochondrial impairment, which activated endogenous cytoprotective mechanisms, including autophagy.

In the present study we aimed at comparing the cytoprotective activities of resveratrol with those of its hydroxylated and methylated derivatives in order to elucidate the structural requirements underlying cytoprotection and identify a compound with improved drug-like properties. Cell culture models were used to investigate mitochondrial effects, autophagy induction, antioxidant activity, and insulin-sensitizing properties.

In cellular degeneration models, resveratrol exhibited dose-dependent cytoprotective effects through the simultaneous induction of mild mitochondrial impairment and antioxidant activity. It also stimulated autophagy, which contributed to improved cell viability and insulin sensitivity, likely by facilitating the removal of damaged organelles. Oxyresveratrol, which contains an additional phenolic hydroxyl group, displayed enhanced antioxidant activity, resulting in pronounced cytoprotective and neuroprotective effects and improved insulin resistance. In contrast to resveratrol, these effects occurred without significant alterations in mitochondrial function or autophagy. Monomethyl resveratrol showed the greatest similarity to the parent compound. However, autophagy induction was delayed and appeared to play a less prominent role in its cytoprotective activity. The possibility that conversion of monomethyl resveratrol to resveratrol contributes to its action cannot be excluded. Trimethylated resveratrol, which lacks free phenolic hydroxyl groups, exhibited markedly reduced cytoprotective activity. This derivative produced stronger mitochondrial damage and a more pronounced prooxidant effect. Although it strongly stimulated autophagy, this response resulted in only partial cytoprotection.

Taken together, our findings demonstrate that resveratrol derivatives share individual components of the cytoprotective mechanism of the parent compound, but none of them fully reproduces its characteristic mode of action. Free phenolic hydroxyl groups appear to be important for antioxidant activity, whereas they are less critical for mitochondrial impairment and autophagy induction. The cytoprotective activity of oxyresveratrol appears to be primarily driven by its enhanced antioxidant capacity, whereas the reduced efficacy of trimethyl resveratrol may be related to its pronounced prooxidant and mitochondrial-damaging properties. Resveratrol itself is characterized by a delicate balance between mild mitochondrial stress and antioxidant activity. This interplay may underlie its preconditioning-like cytoprotective mechanism and represents an important consideration for the development of resveratrol-based therapeutic compounds.

ORAL PRESENTATIONS

DICLOFENAC SODIUM–BOSWELLIA SERRATA NANOEMULGEL FOR TOPICAL ANTI-INFLAMMATORY DELIVERY: DEVELOPMENT AND PHYSICOCHEMICAL EVALUATION

Tutku Su Akbulut, Nailla Jiwa
Near East University, Nicosia, Turkish Republic of Northern Cyprus

Osteoarthritis and rheumatoid arthritis cause persistent pain, joint stiffness, and progressive tissue damage requiring long-term pharmacological management. Topical NSAIDs like diclofenac sodium avoid the gastrointestinal and cardiovascular risks of systemic use, but conventional topical preparations often fail to achieve sufficient drug concentrations in deeper inflamed tissues. Nanoemulgels present improved skin contact time and drug solubilization compared to conventional gels, but their translation into clinically approved NSAID products has not been achieved. Boswellia serrata extract has shown anti-inflammatory and analgesic effects in clinical trials for arthritis, was therefore selected for co-formulation with diclofenac sodium. This study aimed to develop and comparatively evaluate diclofenac sodium nanoemulgel formulations incorporating Boswellia serrata extract, and to assess the influence of Boswellia inclusion on key physicochemical attributes. Three diclofenac sodium nanoemulgel formulations were prepared and compared: NE-B containing Boswellia serrata extract, NE-O and NE-W as Boswellia-free controls compensated with additional oil phase or water, respectively. Nanoemulsions were prepared using a lipid-based oil phase with penetration enhancers and a surfactant mixture, then incorporated into a Carbopol 940 gel base at a 1:1 ratio. Formulations were characterized for pH, viscosity, zeta potential, optical microscopy, and diclofenac sodium entrapment efficiency (EE) by UV–Vis spectrophotometry at 276 nm; *in vitro* drug release was evaluated using the dialysis bag method. NE-B had a pH of 6.47, viscosity of 360 cP, and EE of 87.9%. NE-O showed the highest viscosity (1152 cP) and EE (91.13%) with a pH of 6.89, while NE-W had notably lower EE (54.2%), a viscosity of 388 cP, and a pH of 6.75. The low EE in NE-W suggests that increasing the aqueous phase reduces diclofenac sodium retention by favoring drug partitioning into the external water phase. Based on these results, the lipophilic contribution of Boswellia serrata to the oil phase appears to support drug retention in NE-B, indicating its role not only as an active ingredient but also as a functional formulation component. To our knowledge, this is the first nanoemulgel co-formulation combining diclofenac sodium and Boswellia serrata for topical delivery, and these findings may guide future studies on dermal permeation and the synergistic anti-inflammatory potential of the two actives.

BEHIND THE NUMBERS: NEW FOCUS IN DRUG UTILIZATION (QUALITATIVE STUDIES)

Ria Benkő
Institute of Clinical Pharmacy, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary

Drug utilisation research (DUR) is a broad discipline, it utilise different data sources and study designs with the ultimate aim of promoting rational drug use. Beside the quantitative aspects, which use numerical data to e.g. measure, explain, predict drug use it also encompass qualitative methods to get in-depth insights into different perspectives of drug use. With the new definition of DUR „Quantitative and qualitative studies to describe, evaluate. understand and improve the use of medicines" the importance of qualitative studies has been emphasized.

The aim of the presentation:

1. Define Drug Utilisation Research and its application fields in pharmacy practice
2. Show the main differences between quantitative and qualitative studies
3. List the methods used in qualitative studies
4. Show the variety of contexts and foci of qualitative methods

SPECIAL CHALLENGES OF PEDIATRIC DRUG TRIALS (KEYNOTE)

Csaba Bereczki
University of Szeged, Szeged Hungary

Pediatric drug trials involve unique scientific, ethical, regulatory, and practical challenges. Growth

and maturation substantially influence pharmacokinetics, pharmacodynamics, dosing requirements, and treatment response, making simple extrapolation from adult studies unreliable. Trials are further complicated by small and heterogeneous populations, recruitment difficulties, age-specific endpoints, formulation issues, and the need to minimize invasive procedures.

Specific regulatory frameworks have therefore been introduced. In the European Union, Regulation (EC) No 1901/2006 on medicinal products for paediatric use requires early consideration of pediatric development through a Paediatric Investigation Plan (PIP). In the United States, the Pediatric Research Equity Act (PREA) allows the FDA to require pediatric studies, while the Best Pharmaceuticals for Children Act (BPCA) provides incentives for conducting requested pediatric investigations. Internationally, ICH E11(R1) provides key scientific and ethical principles for pediatric drug development.

Modern approaches - including population pharmacokinetics, modelling and simulation, sparse sampling, adaptive designs, and justified extrapolation from adult data - can reduce patient burden while maintaining scientific validity. The central challenge is to protect children both from unnecessary research risks and through high-quality research, ensuring safe, effective, and evidence-based pharmacotherapy throughout childhood.

3D AND 4D PRINTING AS PROMISING TECHNOLOGIES FOR INNOVATIVE AND PERSONALIZED PHARMACEUTICALS FOR CANCER (KEYNOTE)

Erem Bilensoy
Department of Pharmaceutical Technology, Faculty of Pharmacy, Hacettepe University, Ankara, Türkiye

Additive manufacturing, particularly three-dimensional (3D) and emerging four-dimensional (4D) printing technologies, is increasingly recognized as a transformative approach for the future of pharmaceutical manufacturing and compounding. Conventional pharmaceutical production relies on centralized, large-scale batch processes designed for standardized medicines with fixed doses and API combinations, strictly limiting flexibility for individualized therapies. In contrast, 3D printing enables the fabrication of drug products with precise control over geometry, internal structure, dose, and spatial distribution of active pharmaceutical ingredients, supporting the growing paradigm of personalized medicine.

Considering the literature and patent databases, several pharmaceutical printing technologies including fused deposition modeling, semi-solid extrusion, inkjet printing, and stereolithography have been investigated to produce dosage forms such as tablets, films, gummies, suppositories, implants, and drug-eluting devices. These techniques allow the design of complex dosage forms, multi-drug polypills, and tailored drug release profiles. Regulations are also following up on pharmaceutical printing such as the 2017 FDA guideline describing additive manufacturing and the recent 2026 EMA Q&A document. As these technologies and products mature, pharmaceutical manufacturing may gradually shift toward more flexible and decentralized environments, including hospital pharmacies. In this evolving model, pharmacists will play an increasingly important role in digital formulation design, on-demand manufacturing, quality assurance, and regulatory oversight of printed medicines. In this lecture some examples on 3D and 4D printed drug delivery systems and dosage forms including gummies, intrauterine devices, bioadhesive films, gastroretentive floating platforms and smart implants developed in our lab will be discussed further.

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ORAL DELIVERY OF CALCIUM BUTYRATE: COMPARISON OF BULK FORM AND WATER-IN-OILMICROEMULSION SYSTEM

Emre Şefik Çağlar[1], Mehmet Evren Okur[2], Liban Barre[3], Mustafa Sinan Kaynak[4], Neslihan Üstündağ Okur[5]
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Butyric acid and its salts have attracted considerable scientific interest owing to their roles in gut epithelial maintenance, immune modulation, and colonocyte energy metabolism. Among these, calcium butyrate (CAB) stands out as a promising candidate for oral supplementation; however, its clinical translation is impeded by inherent physicochemical drawbacks including gastric instability, high volatility, and an unpleasant organoleptic profile that compromises patient adherence. The present study therefore sought to engineer a water-in-oil (W/O) microemulsion loaded with CAB (ME-CAB), in which hydroxypropyl-β-cyclodextrin (HPβCD) was incorporated into the aqueous dispersed phase to simultaneously improve sensory masking and formulation stability. Beyond physicochemical optimization, the study extended to mechanistic evaluation of drug release and intestinal transport, providing a comprehensive assessment of the platform's oral delivery potential.

Formulation screening was guided by pseudo-ternary phase diagrams constructed through aqueous titration, enabling systematic identification of stable microemulsion domains. Cinnamon oil was selected as the oil phase, while Span 80 and Kolliphor PS80 formed the surfactant pair and PEG 400/ethanol served as the cosurfactant. A 5% HPβCD solution constituted the aqueous phase. The resulting formulations were characterized with respect to droplet size, polydispersity index (PDI), refractive index, pH, viscosity, transmittance, conductivity, and drug content. Release behavior was investigated in simulated gastric fluid (pH 1.2, 37°C) via the dialysis bag technique, with profiles modeled using zero-order, first-order, Higuchi, and Korsmeyer–Peppas equations. Intestinal permeability was assessed through in situ single-pass intestinal perfusion (SPIP) in rat jejunum (n=6); metoprolol and phenol red were employed as high-permeability and non-absorbable markers, respectively, to derive effective permeability coefficients (Peff) and predicted human fractional absorption (Fa).

The optimized ME-CAB exhibited a droplet size of 9.23±0.97 nm with a PDI of 0.141±0.004, indicative of a narrowly distributed, thermodynamically favorable nanosystem. Drug encapsulation efficiency reached 99.43±0.66%, confirming quantitative incorporation of CAB into the formulation. Release kinetics conformed to the Higuchi model, reflecting matrix-diffusion-governed transport. Whereas a plain CAB solution released over 95% of its content within one hour under gastric conditions, ME-CAB sustained release to approximately 60% at the two-hour mark, demonstrating a meaningful retardation of premature drug exposure. SPIP experiments revealed that, although ME-CAB permeability was moderately lower than that of the free CAB solution, absorption remained at a therapeutically relevant level, consistent with the controlled-release design intent.

The findings collectively demonstrate that microemulsification, combined with HPβCD-mediated odor masking, constitutes a viable strategy for overcoming the principal barriers to oral CAB delivery. The resulting system offers controlled gastric release, preserved intestinal absorption, and improved acceptability, positioning ME-CAB as a sound foundation for further development in therapeutic areas such as inflammatory bowel disease, colorectal health, and microbiome-targeted interventions.

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Key Words: Butyric Acid, Microemulsion, SPIP, Oral Delivery

NADOLOL LOADED SELF EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS) FOR ORAL DELIVERY: FORMULATION, CHARACTERIZATION, IN VITRO CELL AND IN SITU SINGLE PASS INTESTINAL PERFUSION STUDIES

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Nadolol (NDL) is a non-selective beta-blocker classified as BCS Class III, characterized by high solubility but low intestinal permeability. With an oral

bioavailability of only approximately 30%, therapeutic optimization of NDL remains a significant clinical challenge. Self-emulsifying drug delivery systems (SEDDS) represent a promising nanocarrier strategy capable of enhancing oral bioavailability through mechanisms including avoidance of first-pass metabolism, lymphatic absorption enhancement, inhibition of P-glycoprotein-mediated efflux, and generation of nano-sized droplets with high surface area. The objective of this study was to develop and evaluate optimized NDL-loaded SEDDS formulations for improved oral delivery. Excipient selection was guided by solubility screening. A pseudo-ternary phase diagram was constructed using the water titration method to identify optimal component ratios. Two formulations were prepared: S1 (Tween 20 / Transcutol HP:Capryol 90) and S2 (Tween 20 / Transcutol HP:propylene glycol), both incorporating cinnamon oil as the oil phase. Formulations were characterized for droplet size, PDI, zeta potential, viscosity, pH, refractive index, transmittance, self-emulsification efficiency, and thermodynamic stability. Storage stability was assessed over 12 months under refrigerator (4°C), ambient (25°C/60% RH), and accelerated (40°C/75% RH) conditions. *In vitro* drug release was evaluated at pH 1.2 and 6.8 using dialysis membranes. Permeability was assessed in Caco-2 cell monolayers using radiolabeled formulations (Tc-99m), and cytotoxicity was determined via the MTT assay. In situ single-pass intestinal perfusion (SPIP) studies were conducted in Sprague Dawley rats to determine effective permeability (Peff) and predict human intestinal absorption.

The S2-NDL formulation was selected as optimal. Droplet size, PDI, and zeta potential were 0.72 ± 0.04 nm, 0.31 ± 0.02, and −5.31 ± 4.82 mV, respectively. No significant changes in physical parameters were observed throughout 12 months of storage. Complete (100%) drug release was achieved in both gastric (pH 1.2) and intestinal (pH 6.8) media. Caco-2 permeability studies demonstrated that S2-NDL achieved approximately 90% apical-to-basolateral transport, compared to less than 40% for S1-NDL, while TEER changes remained below 40%, confirming cell monolayer integrity. Cell viability exceeded 95% for all formulations, indicating biocompatibility. In SPIP studies, S2-NDL yielded a rat Peff of $0.301 \pm 0.076 \times 10^{-4}$ cm/sec, a 13-fold increase over pure NDL solution ($0.023 \pm 0.012 \times 10^{-4}$ cm/sec). The predicted human Peff (1.114×10^{-4} cm/sec) and estimated fraction absorbed (Fa ≈ 71%) were comparable to the high-permeability reference compound metoprolol (Fa ≈ 77%), indicating a transition of NDL toward BCS Class I-like permeability behavior.

The developed SEDDS formulation incorporating cinnamon oil, Tween 20, Transcutol HP, and propylene glycol demonstrated excellent physicochemical stability, complete drug release, and a marked enhancement in intestinal permeability both *in vitro* and in situ. The 13-fold improvement in Peff and the predicted human Fa of ~71% underscore the potential of this system to overcome the key limitation of NDL's oral bioavailability. This study supports SEDDS as a clinically viable and patient-centered strategy for the reformulation of low-permeability cardiovascular drugs, fully aligned with the conference theme of translating pharmaceutical innovation into improved therapeutic outcomes.

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Keywords: Nadolol, SEDDS, Oral Bioavailability, Single-Pass Intestinal Perfusion, Nanocarrier

PREPARATION AND IN VITRO CHARACTERISATION OF ORALLY DISINTEGRATING FILMS CONTAINING NYSTATIN-PEG SOLID DISPERSION FOR THE TREATMENT OF ORAL CANDIDIASIS USING THE ELECTROSPINNING METHOD

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Nystatin is a well-known antifungal drug and is classified as Class IV according to the Biopharmaceutical Classification System (BCS). It is also widely used in the treatment of oral candidiasis. Although nystatin is insoluble in water and ethanol, aqueous suspensions or tablet formulations are used in the treatment of oral candidiasis (1). Nystatin's low solubility in water may reduce its efficacy in the treatment of candidiasis (2). To overcome this drawback, orally disintegrating films (ODFs) containing nystatin have been developed using the electrospinning method. Eudragit

L 100-55, a polymer that dissolves at pH >5.5, was selected because of the pH of saliva shifts towards acidity (<6.8) in oral candidiasis (3). Nystatin and Eudragit L 100-55 were dissolved in an ethanol:water (8:2 v/v) mixture, and films were prepared by electrospinning. However, due to nystatin's low solubility, complete dissolution could not be achieved in the electrospinning solution, and this resulted in the observation of nystatin precipitates on the fibres in scanning electron microscope (SEM) images. To resolve this issue, solid dispersions of nystatin with the hydrophilic polymers polyethylene glycol (PEG) 4000 or PEG 6000 were prepared at various molar ratios. In brief, nystatin and PEG were dissolved in a methanol:dimethylacetamide (8:2 v/v) mixture at the specified molar ratios (1:1, 1:3 mol/mol) and dried in an oven at 30°C. The ODFs of the solid dispersions obtained were prepared using the same method as the nystatin ODFs. Contrary to expectations, reducing the proportion of hydrophilic polymer increased the solubility of nystatin and ensured that the active ingredient was completely encapsulated within the fibres without precipitation. The carriers used in the preparation of the solid dispersions exhibit non-toxic properties. Consequently, the prepared nystatin-containing solid dispersion ODFs did not exhibit any toxic effects on the L929 cell line. However, an increased anticandidal effect was observed in Candida albicans, attributed to the improved solubility. Various characterisation studies conducted on the ODFs (pH, drug loading, folding endurance, disintegration time and dissolution rate) also demonstrate that nystatin-containing ODFs with optimal properties for the treatment of oral candidiasis have been obtained.

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Keywords: nystatin, polyethylene glycol (PEG), solid dispersion, orally disintegrating films, electrospinning, oral candidiasis

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NANOSTRUCTURED LIPID CARRIERS ENHANCE SKIN DELIVERY AND ANTIPSORIATIC EFFICACY OF TAZAROTENE COMPARED WITH NANOEMULSIONS

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Tazarotene is a third-generation topical retinoid used in the treatment of psoriasis. However, its high lipophilicity and potential for skin irritation may limit dermal penetration, skin bioavailability, and therapeutic efficacy. Overcoming the stratum corneum barrier while minimizing adverse effects remains a major challenge in topical psoriasis therapy. Nanocarrier-based delivery systems, particularly nanostructured lipid carriers (NLCs) and nanoemulsions (NEs), enhance drug penetration, improve skin retention, and provide controlled drug release. This study aimed to develop tazarotene-loaded nanostructured lipid carriers and nanoemulsions and to comparatively evaluate their physicochemical properties, stability, *in vitro* release, ex vivo dermal penetration, cellular performance, and *in vivo* antipsoriatic efficacy. A validated HPLC method was developed for the quantitative analy-

sis of tazarotene. Tazarotene-loaded NLCs were prepared with Compritol ATO 888 or Precirol ATO 5 and Labrafac Lipophile WL, while NEs were prepared with Labrafac Lipophile WL and Kolliphor EL via emulsification-ultrasonication. Tazarotene was incorporated into all formulations at 0.1% (w/w). The formulations were characterized for particle size, polydispersity index (PDI), zeta potential, and stability under refrigerated, room temperature, and accelerated conditions. Optimized formulations were then assessed through a stepwise performance evaluation, including *in vitro* drug release and release kinetics, ex vivo dermal penetration using pig skin in Franz diffusion cells, tape stripping, ATR-FTIR analysis, and confocal visualization of skin distribution using Nile red. In addition, *in vitro* cytotoxicity and cellular uptake studies were conducted to evaluate cellular compatibility and internalization, and *in vivo* antipsoriatic efficacy was investigated in a mouse model. As a result, the optimized formulations exhibited nanoscale characteristics, with the NLC showing a particle size of 119.43 nm, PDI of 0.148, and zeta potential of -6.87 mV, and the NE showing a particle size of 146.67 nm, PDI of 0.139, and zeta potential of -15.57 mV, indicating uniform nanosized dispersions. *In vitro* release studies demonstrated that the NLC provided higher and more sustained tazarotene release than the NE, with cumulative release values of 48.15 μg/cm² and 29.48 μg/cm² at 24 h, respectively. Release kinetics analysis showed that the NLC followed the Higuchi model, indicating diffusion-controlled release, whereas the NE exhibited first-order kinetics, suggesting concentration-dependent release behavior. Dermal penetration studies revealed approximately 3-fold greater tazarotene accumulation in the stratum corneum with NLC than NE, indicating superior skin targeting and retention. Confocal microscopy further supported the enhanced skin localization achieved with the NLC formulation. *In vitro* cytotoxicity studies confirmed acceptable biocompatibility, and cellular uptake studies demonstrated efficient internalization, particularly for the NLC system. *In vivo* studies showed increased orthokeratosis and enhanced TIG2 expression, indicating improved antipsoriatic activity. In conclusion, tazarotene-loaded NLCs demonstrated superior performance compared with NEs, with sustained drug release, enhanced skin targeting, and antipsoriatic efficacy. Overall, these findings suggest that NLCs represent a promising lipid-based nanocarrier platform for improving topical psoriasis therapy. This study

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Keywords: Nanostructured lipid carrier, nanoemulsion, tazarotene, drug delivery, antipsoriatic activity

LINKING PHARMACOTHERAPY AND THE DIGITAL WORLD: OPPORTUNITES, OBSTACLES AND CLINICAL IMPACT

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Introduction: In Hungary, the documentation of patients' healthcare is a legal requirement, including the recording of medication-related interventions. Despite rapid progress in information technology, medication orders in hospitals are still predominantly documented on paper-based charts. To ensure traceability of medication regimens and support patient safety, healthcare documentation must be accurate and reflect the care process chronologically. However, currently available Hospital Information Systems (HIS) in Hungary generally cannot capture medication data in a structured, interoperable, and sufficiently detailed format. This challenge has also been recognised internationally. As a result, most medication-related information remains outside structured digital systems, while the rest is recorded as unstructured free text.

Objective: Comprehensive, itemised, complete, and standardised documentation of medication-related events is essential for monitoring patient care and mapping patient journeys, particularly in chronic conditions. This is especially relevant in psychiatric care, where long-term pharmacotherapy histories (e.g., prior treatment effectiveness in recurrent depression) are critical. The National Laboratory for Translational Neuroscience (NLTN) project aimed to establish large-scale, structured, high-quality data collection in neuroscience to support future healthcare optimisation. Within this framework, a key objective is the standardised, itemised, complete, and longitudinal recording of medication-related events in inpatient care.

Methods: The NLTN Data Platform was used to

conduct a comparative analysis of medication data (e.g., level of structuring and the proportion of structured versus unstructured records) from 2022 and 2025 in a representative patient cohort. The platform contains pseudo-anonymised electronic health data from patients treated at the Clinical Centre of the University of Pécs. Our study focused on psychiatric inpatients.

Results and Discussion: In 2022, inpatient medication data were primarily recorded on paper-based charts, with limited electronic documentation (e.g., drug initiation recorded as free text in progress notes) and additional free-text entries in discharge summaries. In 2024, the existing structured medication module of the HIS was introduced within the NLTN project, enabling daily, itemised, event-level, and longitudinal structured data capture. By the end of 2025, structured medication data had been collected for more than 500 psychiatric patients, representing a shift from limited and predominantly unstructured documentation to routine, daily structured data capture, thereby enabling clearer interpretation of medication regimens.

Despite these advances, important limitations remain. Current HIS lack full compliance with international standards and coding systems (e.g., ATC, SNOMED CT, HL7 FHIR) and do not adequately support structured and standardised documentation of medication-related events (e.g., reasons for therapy changes or discontinuations). These gaps affect terminology, data structure, and interoperability. Consequently, achieving comprehensive, itemised, complete, longitudinal, and standardised medication records remains challenging.

Conclusions: Hospital Information Systems used in Hungary are capable of recording medication data but do not yet fully support standards-based, structured, itemised, and longitudinal documentation. The introduction of structured, event-level data enabled a transition from predominantly unstructured documentation to routine daily recording, improving the interpretability of pharmacotherapy. However, gaps in terminology, data modelling, and interoperability continue to limit the development of comprehensive medication histories. Addressing these limitations could improve patient safety and support advanced analytics using high-quality real-world data.

TARGETING CANCER CELLS BY THE MACROPINOCYTOSIS OF CYCLODEXTRINS

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Cyclodextrins are widely utilized in biological research due to their ability to form complexes with various biomolecules. Recent findings have demonstrated that cyclodextrins can enter cells via endocytosis, offering a novel route for intracellular delivery-particularly relevant in the treatment of cholesterol storage disorders. However, the endocytic uptake of cyclodextrin derivatives across different cancer cell lines has not yet been systematically studied or compared.

In this study, we characterized the physicochemical properties of fluorescein- and rhodamine-labeled derivatives and investigated the endocytosis of fluorescein-labeled hydroxypropyl-β-cyclodextrin (FITC-HPBCD) and random methyl-β-cyclodextrin (FITC-RAMEB) in several distinct cancer cell lines. We also aimed to identify physicochemical and biological factors influencing cellular uptake. Octanol-water partition coefficients and molecular association parameters were determined, revealing significant differences between the fluorescent derivatives of HPBCD and RAMEB. Rhodamine labeling notably altered molecular association and lipophilicity, therefore these derivatives were not used for cellular experiments. Cancer cell lines exhibited marked variability in cyclodextrin uptake, with differential internalization of FITC-HPBCD and FITC-RAMEB observed across the tested models. The expression of KRAS protein and its role in the endocytosis of cyclodextrins were also investigated. *In vivo* tumor accumulation of cyclodextrins was confirmed using radiolabeled derivatives. These findings underscore the potential of cyclodextrins as targeted delivery agents in cancer therapy via the endocytic pathway.

SIMULATION OF POWDER COMPACTION FOR MORE RELIABLE TABLET DESIGN

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Compaction of powders to form tablets is one of the most important steps in the manufacturing of solid formulations. Problems with the end product can often be traced back to tablet compression, therefore it is crucial to achieve an in-depth understanding of this process. Mathematical modelling based on the finite element method (FEM) can be utilized to simulate the compaction process relying on the physical description of elastic and plastic deformation. With this approach, several experiments performed on a compaction simulator can be used to calibrate a model that can act as a digital twin, enabling virtual experiments to substitute laboratory work. The FEM technique can simulate objects of any size and shape, therefore the same model can be used to study various tablet sizes and shapes of the same composition.

The FEM has been used to predict the distribution of porosity in the tablet, the results show good agreements with X-ray CT measurements. The simulation also yields a distribution of the stress in the tablet structure. This approach can be used to study the effect of lubrication on the structure of the resulting tablets. The FEM can also give insight into how the tablet behaves during diametrical compression or friability testing. The structure of the simulated tablets can explain why certain manufacturing settings result in inferior products. For example non-ideal tableting conditions can result in tablets that have higher porosity near the edges, these experience higher weight loss during the friability test. The inhomogeneity of the internal structure can also explain different behaviours during disintegration testing. Moreover, the internal tablet structure predicted by the compression simulation can be used as a starting point by additional models that describe the drug release from a sustained release formulation. In this case, the FEM is used to simulate water ingress, drug dissolution and diffusion out of the tablet.

This modelling approach can be used to design more robust compaction processes, enabling the manufacturing of tablets with good and consistent quality. Implementing this approach into the development workflow of new products can reduce time to market and prevent problems during commercial manufacturing.

TRYPTOPHAN METABOLISM IN MIGRAINE

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Migraine remains one of the most debilitating neurological disorders worldwide. Decades of research have demonstrated that central and peripheral sensitization diminish the threshold of nociceptive pathways making the migraine brain more sensitive to environmental triggers even to stimuli in headache-free periods. Emerging evidence suggests that the tryptophan (TRP) metabolic pathways, serotonin and kynurenine pathways play a key role in hypersensitivity. Kynurenine (KYN) metabolites are modulating glutamatergic neurotransmission that facilitates central sensitization, neurogenic inflammation, and promotes the release of calcitonin gene-related peptide (CGRP) from trigeminal nerve fibers, which has become the primary target for new migraine medications. Despite its importance, clinical data regarding TRP concentrations in migraineurs remain contradictory. Furthermore, the relationship between peripheral TRP metabolism and functional connectivity of pain networks requires further clarification.

In our study, we investigated the association between TRP pathway and pain matrix, specifically focusing on periaqueductal gray matter (PAG) network using resting-state functional MRI. We also measured plasma TRP, KYN and large neutral amino acids (LNAA) concentrations in episodic migraine patients without aura and sex-matched healthy controls during an acute neuroendocrine stress challenge induced by acute citalopram infusion.

Our findings revealed significantly elevated plasma TRP concentrations and TRP/LNAA ratios in migraine patients compared to controls. Nota-

bly, a decreasing KYN/TRP ratio was associated with increased migraine frequency. During the citalopram challenge, healthy controls exhibited physiological adaptive changes in the TRP pathway, whereas migraine patients failed to show this metabolic adaptation. The citalopram-induced alterations in KYN pathway were linked to migraine attack frequency, reinforcing the role of the KYN pathway in maladaptive stress responses of migraine patients. Our neuroimaging analysis demonstrated that plasma TRP levels, corrected for LNAA, were significantly associated with altered functional connectivity between the PAG and „fear-cascade" regions. Furthermore, TRP concentration modulated the connectivity between the PAG and the prefrontal cortex, a circuit found to be correlated with depressive symptoms and trait anxiety-common comorbidities in migraine populations.

Our studies provide robust evidence for systemic dysregulation of the TRP-KYN pathway in episodic migraine patients. The observed insufficient adaptation of TRP and KYN pathways during acute stress supports the hypothesis of maladaptive stress response in migraine. The association found between peripheral TRP and PAG functional networks suggest that TRP metabolism contributes to the hypersensitivity of the migraine brain. Our results support the notion that the KYN pathway may represent a promising therapeutic target for migraine-related hypersensitivity and depressive-symptoms associated with migraine.

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FLURBIPROFEN-LOADED GUMMY TABLETS: A PATIENT-FRIENDLY STRATEGY FOR INDIVIDUALS WITH SWALLOWING DIFFICULTIES

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Dysphagia (difficulty swallowing) is a condition that prevents oral medication administration, particularly in children, the elderly, and certain patient groups with neurological disorders, and leads to decreased patient compliance with traditional solid dosage forms such as tablets and capsules. Flurbiprofen (Flu) is a propionic acid derivative nonsteroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, chronic and acute rheumatic pain and diseases, and dysmenorrhea. In this study, flurbiprofen-loaded gummy tablet (FluGT) formulations were developed as a patient-friendly alternative oral dosage form combining ease of use with acceptable mechanical and physicochemical properties. The formulations were developed via a controlled heating and molding process, followed by cooling under standardized conditions to ensure uniform gel formation. The formulations were prepared using different ratios of gelatin as a gelling agent, different ratios of propylene glycol (PG) for flexibility, stabilization and solubilizing agent, mannitol as a sweetener, orange essence as a flavoring agent, propyl paraben as a preservative, polyethylene glycol 400 (PEG 400) as a solubility enhancer, and distilled water as a solvent. The developed gummy tablets were subjected to comprehensive analysis including morphological controls, weight variation, length-width-height measurements, pH determination, disintegration time determination in distilled water and artificial saliva, moisture determination, and in vitro dissolution rate controls. Among 20 different formulations, the formulation FluGT-F14 (containing 100 mg flurbiprofen, 20% gelatin, 10% PG, 1% aspartame, 1% orange flavor, 1% propyl paraben, and 1% PEG 400) showed a homogeneous appearance, a weight of 1.334 + 0.065 g, disintegration in distilled water in 1 minute 8 seconds, and disintegration in artificial saliva in 1 minute 24 seconds, with an average pH value of 5.3. Texture analysis revealed that the FluGT-F14 gummy tablets exhibited quite good flexibility and tensile strength. The quantitative determination method was validated by obtaining flurbiprofen peaks at a wavelength of 247 nm using UV spectrophotometer. Dissolution studies were performed on commercial flurbiprofen tablets (conventional) and the developed FluGT-F14 tablet at pH 7.2 according to USP, and similar dissolution results were obtained to the commercial tablet. In conclusion, flurbiprofen-loaded gummy tablets offer a promising alternative to traditional oral dosage forms, particularly for adult patients with swallowing difficulties. These findings support the potential of gelatin-based systems as innovative platforms for patient-friendly and require further in vivo studies. ACKNOWLEDGEMENT: This research was supported by The Scientific and

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DEVELOPMENT AND CHARACTERIZATION OF VEGAN LEVETIRACETAM GUMMIES AS A NOVEL PATIENT FRIENDLY DOSAGE FORM

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Introduction**:** Gummies are next-generation chewable gels that are used for the delivery of drugs, nutritional supplements, and other active ingredients. Gummies are patient-centered dosage forms that offer high compliance among certain patient groups (particularly pediatric patients) due to their chewable texture, ability to mask taste, and ease of use. Vegan gummies produced from plant-based polymers such as alginate and pectin have offered numerous advantages in recent years as a sustainable and eco-friendly dosage form [1, 2]. Levetiracetam, which was used as a model drug in this study, is an antiepileptic drug used in a wide range of patient groups [3].

Objectives**:** The primary objective of this study was to develop vegan gummy formulations containing levetiracetam and to characterize the obtained formulations.

Methods: To prepare the gummy formulations, four different formulations containing varying ratios (1–4%) of the pectin:alginate polymer mixture (3:1) were prepared. The formulations were coded as F1-F4. For this purpose, the polymer mixture was gelled in distilled water at 70°C under magnetic stirring, and other excipients were added to the mixture. Subsequently, levetiracetam was added to the hydrogel mixture as it cooled, and mixing was continued until a transparent mixture was obtained. The viscosity of the hydrogel mixtures was measured using a rotational viscometer, and the mixtures were then poured into molds to form gummies.

The diameter, thickness, and weight of the prepared gummies were measured as physical properties. The hardness and elasticity of the gummies were characterized using a texture analyzer.

An *in vitro* drug release study was carried out for gummy formulations. Studies were performed using USP type I dissolution apparatus at 37± 0.5°C and rotation speed of 100 rpm.

Results and Discussion: All formulations (F1-F4) were manufactured successfully. The diameter and thickness of the optimum gummy formulation were found to be 9.6±0.1 and 19.8±0.3 mm, respectively. All gummy formulations had an average weight of approximately 2.5 g. It is important for gummies to have optimum hardness and elasticity so that they are easy to chew and mechanically durable. The hardness and elasticity values of the optimum formulation were determined as 16.2 ± 1.6 N and 1.76 ± 0.09 mm, respectively. The optimum gummy formulation released more than 90% of levetiracetam within 45 min.

Conclusion: The innovative vegan drug gummy formulations developed in this study are promising in terms of their potential for use, particularly in specific patient populations such as pediatrics and geriatrics, by ensuring high patient compliance and facilitating personalized treatment, as well as being eco-friendly.

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A BUCCAL MRNA LNP DELIVERY PLATFORM: A NEEDLE-FREE ALTERNATIVE TO VACCINATION

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Recent global health challenges, most notably the COVID-19 pandemic, have underscored the criti-

cal role of biopharmaceuticals in addressing both acute and chronic medical needs. The rapid development of nucleic acid–based vaccines highlighted not only their transformative therapeutic potential but also key technological limitations related to manufacturing scalability, cold-chain dependence, and patient-friendly administration. At the same time, long-term epidemiological trends have driven increasing demand for biomolecules as active pharmaceutical ingredients, including mRNA-based therapeutics. These recent developments emphasize the urgent need for integrated formulation and delivery platforms that ensure stability, efficacy, and accessibility.

Biological drugs are structurally complex and inherently sensitive macromolecules. Their instability arises from susceptibility to aggregation, enzymatic degradation, hydrolysis, and conformational changes throughout manufacturing, storage, and administration processes. Nanoparticle-based delivery systems — particularly lipid nanoparticles (LNPs) — provide the ability to encapsulate nucleic acids and protect them from degradation, combined with controlled release capabilities, making them ideal candidates for mRNA delivery. However, a limitation of current mRNA-LNP technologies is their dependence on ultra-cold storage.

Cold-chain requirements significantly hinder global vaccine distribution, especially in low-resource settings. Solid-state stabilization could mitigate these constraints, enabling room-temperature storage and improved pandemic preparedness. Conventional liquid formulations, while widely used, present significant logistical challenges, including cold storage requirements and reduced patient compliance. Solid-state stabilization techniques such as freeze-drying and spray drying offer alternatives but are often limited by stress-induced damage to biomolecules. High-speed electrospinning was demonstrated as a robust platform technology for the successful preservation of enzymes, antibodies, nucleic acids, and probiotic bacteria.

Beyond formulation stability, the route of administration represents another critical bottleneck in biologic therapy. Oral delivery remains the most widely accepted and patient-compliant route; however, its applicability to biologics is limited by gastrointestinal barriers. Consequently, alternative mucosal administration routes have gained attention. Among these, buccal delivery offers unique physiological advantages. The buccal mucosa exhibits relatively low enzymatic activity and maintains a near-neutral pH environment, all of which favor biomolecule stability. Moreover, transmucosal absorption enables direct systemic entry, bypassing hepatic first-pass metabolism.

In this study, a buccal delivery platform was developed for the efficient delivery of mRNA-LNP coding GFP as a model protein. For this purpose, electrospinning was used as a gentle drying technology preserving mRNA efficiency in the solid formulation. The integration of advanced formulation strategies with innovative delivery routes, including buccal delivery systems, holds significant promise for enabling efficient biologics. Such approaches could improve patient compliance, and reduce reliance on cold-chain logistics. Ultimately, the development of scalable, continuous manufacturing technologies will be key to enhancing the efficiency, affordability, and global availability of next-generation biopharmaceuticals.

SIGMA-1 RECEPTOR IS A NEW ANTI-GLAUCOMA TARGET: PRECLINICAL DEVELOPMENT OF A NOVEL EYE-DROP

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Background: Glaucoma is the leading cause of blindness, but current treatments are only partially effective and have many side effects. Elevated intraocular pressure (IOP), the primary risk factor is directly linked to trabecular meshwork (TM) fibrosis. We published and patented that the Sig-

ma-1 receptor (S1R) agonists fluvoxamine (FLVX) reduces fibrotic processes in various tissues, including the eye. Here, we developed a FLVX-containing eye drop and investigated its mechanism of action, tolerability and therapeutic efficacy in preclinical settings.

Methods: S1R abundance, ER stress, TM stiffness and outflow were investigated in human tissue and in TGFβ2-treated HTM5 cells. Local tolerance tests of the eye drop were performed in mice and rabbits, while efficacy in lowering IOP and restoring vision was assessed in different glaucoma models using wild-type (WT) or S1R-/- mice or rats treated daily with FLVX-containing eye drops (100 mM) or vehicle for 2 or 4 weeks. S1R, FLVX concentration, and fibrosis-related proteins were also measured in the eyes.

Results: S1R is localized in the TM across all species. FLVX minimizes TGF-induced ECM accumulation, reduces IRE-1, Xbp-1, pERK levels, while increasing NO release. The preservative-free, FLVX-containing eye drop is well-tolerated, penetrates through the cornea and remains stable for a year at RT. It reduces IOP by 39.1% in glaucomatous rats and by 19.6% in WT mice, while it has no effect in S1R-/- mice. In parallel, FLVX improves visual acuity and contrast sensitivity in glaucomatous rats (by 12.8% and 35.8% resp). FLVX eye drop reduces fibrosis, confirmed by lower levels of TGFβ2, αSMA, fibronectin and collagens in mice TM.

Conclusions: S1R is a novel anti-glaucomatous target. The S1R agonist FLVX-containing eye drop is safe and non-irritating, improves vision and restores increased IOP by reducing ocular fibrosis and enhancing outflow. Based on these extensive preclinical data, the phase I/II clinical study will start in 2026 autumn.

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MANAGING MEDICATION SAFETY: EVIDENCE FROM HOSPITALS AND COMMUNITY CARE

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Preventable medication-related harm remains a major global patient safety challenge, affecting approximately one in twenty patients and accounting for substantial morbidity, mortality, and healthcare costs. Effective management of medication safety requires a system-level understanding of where and why harm occurs, across the entire medication-use process and in different care settings. This keynote synthesizes evidence from hospital and community care to highlight core risk points, high-risk patient groups, and medicines that should be prioritized in medication safety management.

Drawing on a series of register-based and observational studies conducted in Finland, the presentation first examines medication errors in pediatric hospital care, with a particular focus on high-alert medications. Analysis of medication error reports from a pediatric university hospital demonstrates that high-alert medications are disproportionately associated with patient harm and higher risk classifications. Errors most frequently occur during prescribing and administration, especially with intravenous medicines. A small number of drugs—such as parenteral nutrition, hypertonic sodium chloride, potassium chloride, opioids, and anticoagulants—account for a large share of serious and severe events, underlining the need for targeted preventive strategies. Evidence on system defenses, including computerized physician order entry and clinical decision support tools, is discussed in relation to their potential to reduce dose-related and high-severity errors.

While medication safety research has long focused on hospitals and specialized care, increasing attention has been directed toward community settings in recent years. In community care, especially pharmacies play a critical role in managing medication safety of patients. National data from a six-year dispensing error register illustrate how changes in dispensing practices, digitalization, and mandatory verification systems have influenced medication safety in Finland. Although the overall number of reported dispensing errors have decreased markedly over time, particularly after the implementation of electronic verification, the persistence of wrong-strength and multidose-related errors highlights ongoing vulnerabilities. Importantly, patients themselves detect a substantial proportion of dispensing errors, emphasizing their role as active contributors to medication safety.

Across both settings, the findings reinforce that safe pharmacotherapy is not solely a drug-related issue but a complex interaction between systems, professionals, patients, and technologies. The

presentation concludes by arguing for a proactive, multi-professional approach to medication safety management, prioritizing high-risk medicines, vulnerable populations such as pediatric and older adults, and high-risk environments. Evidence-informed system defenses, combined with continuous learning from error data, are essential to achieving safer pharmacotherapy across the continuum of care.

AUTOMATED SEMI-SOLID EXTRUSION PRINTED ZOPICLONE TABLETS FOR DOSE TAPERING FOR WITHDRAWAL MEDICATION REGIMEN

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Introduction: Zopiclone is a non-benzodiazepine hypnotic indicated for short-term treatment of sleep disorders not exceeding 2-4 weeks due to their risk of dependence and abuse potential. Currently, the options for zopiclone withdrawal therapy are limited, with no commercially available dosage forms that allow for slow tapering. Pharmaceutical printing is an emerging manufacturing technology that enables the production of patient-specific customisable doses and dosage forms with high precision and flexibility. Compared to traditional compounding techniques, printing is an automated process making manufacturing more efficient and less prone to human error. Printing also allows for in-process controls such as weighing of each tablet for dose uniformity tests, thereby improving overall product quality.

The aim of this study was to provide an automated printing method that allows for safe and customised doses and dose tapering of zopiclone.

Methods and materials: The zopiclone printed tablets were prepared from crushed commercial tablets (Somnols, Grindeks AS) and printing bases using Pharma Printer 1 (CurifyLabs Oy, Finland). Two printing bases – CuraBlend® Gel Tablet (water-based) and Anhydrous Troche CuraBlend® were tested to compare the stability of the water-based and water-free formulations. 0.5% and 1.5% (m/m) zopiclone formulations were made with these bases respectively, to allow for the largest starting doses possible. Prior to printing, the zopiclone crushed tablet powder and printing base were mixed using an automated mixer at 2800rpm. The Anhydrous Troche printing base was pre-heated at 50°C prior to mixing. Tablets were printed at 46°C (Gel Tablet) and 39°C (Anhydrous Troche) into MediDose Mini Medi-Cup® Plus™ Blisters and sealed with LaserLabel Cover Sheets. Different drug doses were obtained by printing different volumes of the mixtures. Weighing and visual assessment as well as high-performance liquid chromatography (HPLC) content analysis of prepared tablets were used for characterisation. Stability studies were carried out up to 1.5 months (sample collection timepoints at 0, 1, 3, and 7 weeks) at room temperature and humidity after which HPLC analyses for content were repeated.

Results: The printing mixtures were visually homogenous after 10 (Gel Tablet) or 20 (Anhydrous Troche) minutes of mixing, allowing for uniform printing of tablets.

Stability testing on the Gel Tablets showed a decrease in concentration of zopiclone, with the tablets containing approximately 36.6% of the target concentration of zopiclone at seven weeks. Anhydrous Troche based tablets showed zopiclone content of 102.9% of the target concentration at 0 weeks with no significant drop at 1 week. Further stability time-points are pending.

Conclusion: The selection of suitable printing base is of relevance for zopiclone, as the presence of water likely affects its chemical stability in printed tablets. Further testing will include further stability data for both formulations, physicochemical characterisation of the tablets, as well as different concentration variations in the Anhydrous Troche based tablets.

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DEVELOPMENT AND CHARACTERIZATION OF AVOCADO OIL AND ROSEHIP OIL CONTAINING MICROEMULSIONS AND MICROEMULSION BASED IN SITU GELS FOR ANTI-AGING APPLICATIONS

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The skin consists of three main layers: the epidermis, dermis, and hypodermis. The epidermis, 0.05–1 mm thick, forms the barrier of the skin and contributes to innate immune defense and protection against ultraviolet (UV) radiation. Skin aging is a complex process characterized by the accumulation of functional changes in cells and tissues due to disruptions in regulatory mechanisms. Both intrinsic factors, including hormonal processes, genetic background, and cellular metabolism, and extrinsic factors, such as UV radiation, environmental pollution, and chemical exposure, play roles in this process. The combined effects of these factors result in fine lines, wrinkles, and structural skin changes. Avocado (Persea americana), a member of the Lauraceae family, has gained attention in pharmaceutical and cosmetic applications due to its bioactive constituents. Avocado oil is considered one of the most valuable derivatives of fruit because of its distinctive organoleptic properties. Carotenoids, chlorophylls, tocopherols, and phenolic compounds found in its unsaponifiable fraction are linked to anti-aging and anti-inflammatory effects. Similarly, rosehip (Rosa spp.), widely used in traditional medicine, is an important source of bioactive compounds for dermocosmetic formulations. Rosehip oil obtained from Rosa canina seeds contains α-linolenic acid, carotenoids, phenolic compounds, and vitamins A, B complex, C, and E. Owing to this composition, it has potential benefits in scar healing, reduction of photoaging signs, and management of hyperpigmentation. To formulate active ingredients such as avocado oil and rosehip oil into topical systems, enhance their permeation through the skin barrier, and improve their biological effects, nanoscale drug delivery systems are needed. Microemulsions are thermodynamically stable, transparent, isotropic systems stabilized by surfactants and cosurfactants. They can carry both lipophilic and hydrophilic components. Their spontaneous formation is related to the negative free energy required for droplet formation, which occurs through a marked reduction in interfacial tension. Easy preparation without external energy, long-term resistance to phase separation, and nanometer-sized droplets make microemulsions advantageous carrier systems. In this study, avocado oil- and rosehip oil-containing microemulsion formulations with increased viscosity at skin temperature were developed, characterized, and evaluated by cell culture studies. During formulation development, the oil phase, surfactant, and co-surfactant were mixed in predetermined ratios, and the optimal microemulsion was selected by a ternary phase diagram. The optimal formulation (ME-5) had a pH of 6.043±0.16, viscosity of 153.33±5.77 cP, droplet size of 23.83±0.919 nm, and zeta potential of -125.95±240.67 mV. To increase viscosity at skin temperature, P407 and P188 were added to the aqueous phase, while 4 drops of lecithin were incorporated into the oil phase. The viscosity-enhanced formulation (ME-IS-4) showed a pH of 5.84±0.067 and viscosity of 420±34.64 cP. Spreadability and texture profile analyses were performed. The hardness and adhesiveness values were -3.513±0.022 g and 6.112±0.607 g·s, respectively. *In vitro* studies showed that the optimal microemulsion formulation was non-cytotoxic. Avocado oil- and rosehip oil-containing microemulsion systems with increased viscosity at skin temperature may be considered innovative and promising carrier systems for anti-aging dermocosmetic applications.

Keywords: Avocado oil, Rosehip oil, Microemulsion, Anti-aging, Skin barrier

TRENDS AND PERSPECTIVES OF TDM

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Therapeutic drug monitoring (TDM) is undergoing a profound transition as a result of the revolutionary improvement in laboratory technology and the emergence of precision pharmacotherapy. As a tool of precision medicine, TDM is becoming a multidisciplinary discipline with tasks for the hospital pharmacy. Supporting patient-centric care efficiently requires dedicated knowledge and competence by pharmacists with related specialized functions. The discussion of the current trends and perspectives which shape TDM into a 21st century field of science and medicine is expected to help the shaping of their personal competence and defining their organizational roles.

The aim of the presentation is to address the following:

1. the context of TDM is already different in various medical specialties, leading to further specialization of TDM professionals in the future;
2. the multidisciplinarity of TDM implies that

hospital and laboratory TDM pharmacists must educate each other and share practical knowledge regarding workflows and institutional protocols;
3. new drugs with highly specific pharmacodynamic targets are becoming available, new indications emerge for existing medications, and increasingly specialized dosing protocols are introduced for various patient populations. Related clinical knowledge is limited; TDM protocols are likely developed in the framework of researcher-initiated clinical studies which involve hospital and laboratory TDM pharmacists;
4. emerging laboratory technology offers novel options like remote sampling or TDM using biosensors, delivering new tasks and frameworks for TDM-guided therapy;
5. The information technology background of healthcare facilities profoundly impacts the efficiency of TDM, a data-driven patient management tool, to assist clinical decision making.

DEVELOPMENT OF NOVEL THIOLATED ALBUMIN NANOCARRIERS FOR IMPROVED LOCAL NASAL ANTIBIOTIC THERAPY

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Amoxicillin is recommended as an oral high-dose regimen as the first-line treatment for acute bacterial rhinosinusitis (ABR). However, the threat of antibiotic resistance is compounded by the intolerable risk of numerous systemic adverse reactions and low oral bioavailability. Accordingly, nasal administration of amoxicillin has emerged as a viable strategy to address these limitations and to treat ABR locally. In this context, mucoadhesion and retention characteristics are crucial to ensure the efficacy of local therapy in the nasal cavity, which is limited by rapid mucociliary clearance. To overcome this, thiolated polymers are used to enhance mucosal retention via covalent disulfide bonding with mucus glycoproteins.

The present study aimed to develop and characterize a novel mucoadhesive drug delivery system for intranasal administration of Amoxicillin-trihydrate (AMT) using cysteine-modified Bovine Serum Albumin (BSA-Cys) as a nanocarrier. BSA-Cys was synthesized by conjugating L-cysteine to BSA at three molar ratios (1:1, 55:1, and 100:1) via EDC/NHS coupling chemistry and was characterized by FT-IR, DSC, TGA, and XRPD. Performance was evaluated through drug-release and mucoadhesion studies.

Comprehensive solid-state characterization (FT-IR, DSC, TGA, and XRPD) confirmed the successful removal of free cysteine and the preservation of an amorphous protein matrix, which is ideal for rapid drug dissolution. Ellman's assay confirmed the presence of accessible thiol groups across all formulations. Thiolated BSA derivatives exhibited significantly superior mucoadhesive properties compared to native BSA. Notably, the 100:1 conjugate achieved adhesive work comparable to 0.5% w/w sodium hyaluronate, a well-known mucoadhesive polymer (58.1 Nm mm), indicating strong resistance to mechanical clearance. *In vitro* release studies demonstrated that the modification sustained drug release in both a pH 5.6 simulated nasal electrolyte solution (SNES) and pH 7.4 PBS. *In vitro* antibacterial studies revealed that the formulation process did not reduce the potency of encapsulated AMT. *In vitro* cytotoxicity studies on NIH cells showed no significant decrease in cell viability, indicating safety for therapeutic application.

It can be concluded that the thiolated albumin platform successfully enhanced the mucosal residence of AMT.

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EFFECT OF CYCLODEXTRIN COMPLEXATION ON THE SIMULTANEOUS SEPARATION OF INSULIN ANALOGUES

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Human insulin is a pancreatic peptide hormone that plays an essential role in blood glucose home-

ostasis. As the number of approved insulin analogues continues to increase, there is a growing need for cost- and time-efficient methods for their quality control. This study aimed to develop and optimize a capillary electrophoresis (CE) method capable of separating human insulin and five of its analogues using successive multilayer ionic layer (SMIL)-coated capillaries. These coatings were evaluated as surface modification strategies to regulate electroosmotic flow (EOF), reduce undesired interactions between insulin analogues and the capillary wall, and improve overall separation selectivity. The insulin analogues were analysed by CE using 33 cm bare fused-silica capillaries. Two types of SMIL-based surface coatings were tested, namely $(PDADMAC/PSS)_{2.5}$ and $(PB/PSS)_2$. Various background electrolytes were screened, and several neutral and anionic cyclodextrins (CDs) were evaluated to enhance selectivity. The effect of organic modifiers at different concentrations was also investigated. Samples were hydrodynamically injected at 50 mbar for 4 s, and detection was performed at 210 nm. Separation performance was significantly improved using dynamically coated capillaries, with results depending on both the surface coating and buffer composition. SMIL-based coatings provided enhanced selectivity, with the $(PB/PSS)_2$ coating outperforming $(PDADMAC/PSS)_{2.5}$. The latter provided only partial resolution in an acetic acid-based background electrolyte supplemented with CDs. In contrast, $(PB/PSS)_2$-coated capillaries further improved selectivity, yielding the most promising results with an ammonium acetate buffer at pH 9 containing (2-carboxyethyl)-β-cyclodextrin. Under these conditions, the six insulin analogues exhibited clearly distinct migration profiles within approximately 5 minutes. In conclusion, SMIL-coated capillaries, particularly the $(PB/PSS)_2$ coating, combined with CD-containing background electrolytes, significantly enhanced separation selectivity in CE. These conditions enabled rapid differentiation of six insulin analogues within a short analysis time.

DISCOVERY OF CASPASE-1 AND CASPASE-6 TARGETED SMALL MOLECULES FOR NEUROINFLAMMATION AND NEURODEGENERATION

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Neuroinflammation is a key contributor to neuronal dysfunction and progressive neurodegeneration, including in Alzheimer's disease. Central to this process is the NLRP3 inflammasome, whose overactivation drives sustained inflammation. Caspase-1 plays a pivotal role by mediating the maturation of the pro-inflammatory cytokines IL-1β and IL-18 and by inducing pyroptotic cell death through gasdermin D cleavage. In parallel, caspase-6 has been implicated in neurodegeneration and axonal pathology, highlighting both proteases as attractive therapeutic targets.

The project aims at discovery of small-molecule inhibitors targeting both caspases using a fragment-based drug discovery (FBDD) approach. This strategy enables the identification of structurally diverse covalent fragments, including chemically novel and underexplored electrophilic warheads, that modulate caspase activity. In addition to active-site engagement, allosteric inhibition is explored as an attractive alternative to achieve improved selectivity and control over caspase function. Lead compounds are being optimized to enhance potency and selectivity and are evaluated for their anti-inflammatory activity in disease-relevant cellular models of neuroinflammation. Overall, this work seeks to deliver new chemical tools to interrogate the roles of caspase-1 and caspase-6 in neuroinflammation and neurodegeneration and to support the development of innovative therapeutic strategies.

DISSOLUTION TESTING USING ELECTROCHEMICAL TECHNIQUES

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Analytical methods used for quantifying drug release in dissolution tests can be classified into three categories: spectrophotometric, chromatographic, and electrochemical.

Electrochemical methods are analytical techniques used to monitor drug release by measuring electrical signals, such as potential-, current-, conductivity-, or impedance-based changes. They are usually „direct" methods in terms that no sample preparation is required, and they are not coupled with other separation or detection techniques. It is particularly useful for rapid dissolution studies,

allowing direct determination of dissolution or release kinetics.

Advantages of electroanalytical methods are

– Real-time Monitoring: Offers in-line capability for continuous tracking, eliminating the need for expensive and time-consuming sampling and/or sample preparation.
– High sensitivity: Can distinguish differences in dissolution times that are too fast for conventional spectroscopy.
– Low Interference: Not affected by suspended particles, turbid samples that interfere with light scattering techniques.
– Potential to be used as a Process Analytical Technology (PAT) tool.
– On the other hand, they have some limitations as well:
– The molecules of interest must be electrochemically active (for voltametric or amperometric detection) or charged (for potentiometric detection).
– They are considered as alternative analytical methods, as spectroscopic and chromatographic methods are primarily accepted by pharmaceutical regulations or quality control (QC).
– Challenging process of validation and acceptance, which is plausible if shown equivalent or superior to compendial methods

In this work, we discuss the analytical performance of electrochemical methods used for accurate drug release measurement, including sensitivity, selectivity, and dynamic range.

Through the example of dissolution testing of levothyroxine-containing suppositories, we demonstrate the advantages and limitations of the voltammetric method. A screen-printed graphene-based working electrode was employed for the measurements. The impact of interfering substances (such as surfactants, suppository bases, etc.) is discussed, along with the corrections required due to changes in the electrode surface. Finally, the successfully implemented experimental setup is presented.

SGLT2 INHIBITORS MODULATE DOXORUBICIN-INDUCED CARDIOTOXICITY

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Doxorubicin (DOX) is an effective anticancer agent, yet its clinical application is restricted by dose-related cardiotoxicity. In contrast, SGLT2 inhibitors like Dapagliflozin (DAPA) and Empagliflozin (EMPA) offer clear cardiovascular advantages, including lower heart failure rates. Despite extensive research into DOX-induced heart damage, the exact molecular signaling behind the protective effects of DAPA and EMPA remains largely unknown.

The objective of this study was to evaluate the cardioprotective potential of DAPA and EMPA within a model of DOX-induced cardiotoxicity. Sprague–Dawley rats were randomized into four experimental cohorts. The DOX group received six intraperitoneal injections of DOX (2.5 mg/kg). In the treatment groups, DAPA (10 mg/kg/day) or EMPA (25 mg/kg/day) was administered via oral gavage, starting prior to and continuing throughout the DOX regimen. Following the treatment period, electrocardiographic (ECG) recordings were performed, and hearts were subsequently isolated for ex vivo functional analysis.

Histological evaluation was performed on cardiac tissue sections using H&E staining to assess general morphology and Masson's trichrome staining to determine the extent of fibrosis. Lipid peroxidation was quantified by measuring cardiac malondialdehyde (MDA) levels. Western blot analyses were conducted to examine key molecular pathways: autophagy-related proteins including p-AMPK/total AMPK, Beclin-1, LC3B, and p62; the FEM1B–FNIP1 axis; and ferroptosis-associated markers, including SLC7A11 and GPx4. Additionally, apoptosis was evaluated in cardiac sections using the TUNEL assay. Together, these methodologies were employed to elucidate the mechanisms underlying the potential cardioprotective actions of DAPA and EMPA in the setting of DOX-induced cardiac injury.

Both DAPA and EMPA successfully ameliorated the cardiotoxic effects of doxorubicin. Key markers of cardiac performance were significantly improved relative to the DOX group, while histological analysis confirmed a decrease in tissue damage and fibrotic remodeling. The intervention also led to a substantial drop in lipid peroxidation and apoptotic cell counts. Additionally, SGLT2 inhibition was associated with the modulation of autophagy-related protein expression. Specifically, DAPA-treated subjects showed an attenuation of DOX-induced ferroptosis. However, additional studies are required to fully elucidate the path-

ways responsible for the distinct outcomes observed between the two SGLT2 inhibitors.

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RAPID SURFACE MAPPING OF PHARMACEUTICAL TABLETS: UV REFLECTANCE IMAGING FOR COMPONENT DISTRIBUTION ANALYSIS

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Vibrational spectroscopic chemical imaging is an essential analytical technique in the pharmaceutical industry, used to characterize materials and pharmaceutical dosage forms. While Raman and near-infrared (NIR) chemical imaging are widely applied for mapping the surface distribution of tablet components, these methods often require long data acquisition times ranging from several minutes to many hours. In this study, UV reflectance imaging-based machine vision is evaluated as a high-throughput alternative to these established spectroscopic techniques.Visually white model tablets containing low-dose spironolactone as the active pharmaceutical ingredient (API), with microcrystalline cellulose (MCC) and lactose monohydrate (LAC) as the main excipients, were investigated. To evaluate the method\'s robustness across various particle dimensions, five separate tablet batches were prepared using a Styl'One Evo compaction simulator. These batches were manufactured from powder blends of identical composition, differing only in the particle size fraction of the spironolactone API (<50 to 300 μm).\r\nImages were taken and analyzed with a benchtop laboratory tablet imaging- and analysis system (TabletScanner by QDevelopment Ltd.) equipped with its UV Chemical Imaging Toolhead. This consists of a camera equipped with a UV-sensitive sensor designed for high-sensitivity direct UV imaging, and a high-intensity, narrow-band UV dome illumination centered at approximately 270 nm.With UV reflectance imaging, the recorded grayscale intensity reflects the balance between absorption and scattering at each surface location. To establish a visual reference for each component, a dedicated reference compact was imaged where pure components were layered separately: spironolactone appeared as the darkest phase due to its strong UV absorption, lactose monohydrate appeared the brightest, and microcrystalline cellulose exhibited an intermediate gray tone. For the actual tablet samples, automatic segmentation and identification of components were performed using k-means clustering based on the mean grayscale values obtained from the reference compact. Images obtained with the TabletScanner provided sufficient grayscale contrast to effectively distinguish the three main components. The software's image analysis platform allowed for a user-friendly method to create the image analysis pipeline, and then apply that automatically for the images. The resulting component maps showed qualitative and spatial agreement with distributions obtained from NIR and Raman imaging. A major advantage of this approach was the speed of acquisition; UV imaging-based chemical mapping required only 0.09 s for a single full-surface exposure, whereas total mapping times for NIR and Raman were approximately 1.3 hours and 83 hours, respectively.These findings support UV reflectance imaging using the QDevelopment TabletScanner as a rapid, automated surface screening tool. By providing high-speed characterization of component spatial distribution, this approach complements slower spectroscopic imaging techniques and facilitates faster decision-making in pharmaceutical formulation development.

FORMULATION OF LIVE VIRUSES WITH ELECTROSPINNING AND ELECTROSPRAYING: NOVEL APPROACH TO ENHANCE ORAL AND PULMONARY VACCINATIONS (KEYNOTE)

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Alternative vaccination routes provide notable advantages over the most widely used parenteral delivery. In addition to the simpler and safer administration, oral and pulmonary application of live

vaccines have the potential of inducing a mucosal immune response at the entry site of viruses. However, formulation challenges limit the efficacy of vaccine delivery through the gastrointestinal and respiratory tract.

Electrospinning and electrospraying are dry formulation technologies that operate at an ambient temperature that is favorable for the formulation of sensitive biologicals. We used a high-speed electrospinning device with upscaled productivity to load live viruses into polymer nanofibers and nanoparticles, and analyzed the product morphology with scanning electron microscopy as well as the stability of virus titers upon production and subsequent storage to prove the potential of these innovations in vaccine production.

Viruses of both DNA or RNA genome, with or without a lipid envelope, well tolerated the nanoformulation processes, using water-soluble biocompatible polymer matrices supplemented with sugar-type additives. During the production of nanofibers, the highest protection of virus infectivity could be achieved with sucrose excipient, whereas in terms of storage stability, mannitol overperformed sucrose in most experimental setups. While there were slight differences between the results gained with viruses of different resistance profiles, infectious titers remained remarkably stable over a 4 month long storage period of the nanoformulated products.

Virus-carrying nanofibers have a great potential for oral vaccine delivery, particularly as feed additives for livestock animals. Electrosprayed nanoparticles are ideal candidates for nasal or pulmonary administration of live virus vaccines. We developed a novel, AI-based automated method of particle size analysis, that significantly simplifies the control of particle size, which is imperative for the most efficient immunization through the airways. With later optimizations to enhance mucoadhesion and bioavailability, the presented formulation approaches might open up new perspectives in veterinary and human vaccinations.

A DUAL-PERSPECTIVE CROSS-SECTIONAL SURVEY OF PHARMACISTS AND PATIENTS. READINESS AND ATTITUDES TOWARDS PHARMACIST PRESCRIBING

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Background: Driven by systemic healthcare challenges, many countries authorized pharmacist prescribing to improve patient access, a shift that enhances public access to treatments. However, this remains an unexamined area in Germany, as current legislation maintains that doctors have the sole right to prescribe.

Objectives: This study aimed to explore the perspectives of both pharmacy customers and pharmacists' views regarding the potential introduction of pharmacist prescribing and whether they could envision its implementation within the current healthcare system.

Methods: In 2023, pharmacists and pharmacy customers in Germany took part in an anonymous online survey. Pharmacists were asked to participate via email, which was sent to over 3,000 pharmacies across Germany, to obtain a nationwide picture of opinion. While pharmacy customers were recruited via convenience sampling, primarily through community pharmacies. A 30 and 28-item questionnaire, respectively, addressing demographic characteristics, core aspects of patient care, and attitudes toward pharmacist prescribing.

Data processing and analysis were conducted using IBM SPSS version 28.0.1.

Results and discussion: Key findings indicate strong support for pharmacist prescribing in Germany. Within the profession, 82.3% of participants held positive views, with 81.8% feeling prepared to take on prescribing roles following advanced training (deemed essential by 85.9%). Results were similarly robust among the public, pharmacy customers: 84.4% of customers expressed high trust in their pharmacists, and 88.0% supported the concept of prescribing rights across all age and gender groups. Additionally, 79.1% of customers emphasized the necessity of formal clinical training for such a transition.

ELECTROSPINNING OPTIMIZATION OF PVA AND ANTIMICROBIAL PEPTIDE-LOADED PVA DRESSINGS

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Background: Chronic wounds and wound infections represent a major challenge for society, as they cause long-term disability, high mortality, and significant healthcare costs [1]. Currently, effective wound treatment options are limited. One promising novel strategy is the fabrication of electrospun (ES) fibrous wound dressings together with antimicrobial peptides (AMPs) to improve wound healing outcomes.

Coaxial ES is a technique in which a dual-channel needle is used to simultaneously ES two different solutions, resulting in fibers with a core–shell structure [2]. Compared to monoaxial ES, coaxial ES enables more efficient encapsulation of therapeutic agents within the fiber, reduces crystallization of active compounds on the fiber surface, and allows for more controlled drug release. In the present study, both conventional monoaxial and coaxial ES approaches were investigated for the incorporation of different AMPs into ES wound dressings in order to identify optimal formulations and processing conditions for stable fiber formation and controlled AMP incorporation.

Aim of the study: To optimize the ES of polyvinyl alcohol (PVA)-based wound dressings and dressings containing different AMPs and characterize these obtained dressings.

Materials and methods: A high-quality hydrophilic polymer, polyvinyl alcohol (PVA; 26 88 and 588), was used for mat fabrication. Both monoaxial and coaxial ES techniques were used to prepare fiber mats. Polymer solutions were prepared by dissolving the polymer PVA in distilled water with the aid of heat (95°C). During ES optimization,PVAs with different molecular weights and various PVA solution concentrations were investigated. The addition of Tween 20, acetic acid and ethanol (96%) into the formulations were additionally evaluated. ES process parameters were varied. Different AMPs were synthesized in KCL (N=6) and used as therapeutic agents. Six AMP-containing fibrous mats were fabricated.

The fibrous mats were visually analysed and weighed, and the morphology of the fibrous mats was analyzed using scanning electron microscopy (SEM). AMP content in fibers was analysed using HPLC and HPLC-MS.

Results: As monoaxial ES resulted in solution dripping or needle sticking despite optimization of the polymer solution composition or process parameters, coaxial ES method was selected for fabrication. A 16% (w/w) PVA (26-88) solution in distilled water was selected as the inner layer, while 96% ethanol solution was used as the outer layer. This method and formulation provided stable and uniform ES. Other formulations tested did not provide stable ES. AMPs were incorporated at 2% (w/w) relative to the polymer weight; the addition of AMPs did not cause major changes in the ESprocess. SEM micrographs demonstrated that the prepared fibers had a uniform morphology and no visible drug crystals were observed on the fibers. AMPs were successfully incorporated into fiber mats via coaxial ES, although some differences in encapsulation efficacy were observed among the AMPs.

Conclusions: The ES process was successfully optimized in terms of both material composition and process parameters. Further studies are needed to evaluate the antimicrobial and wound healing effect of these mats.

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FORMULATION, CHARACTERIZATION AND OCULAR IRRITATION EVALUATION OF A DUAL-COMPONENT (HESPERIDIN–HYALURONIC ACID) OCULAR IN SITU GEL FOR DRUG DELIVERY

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Allergic conjunctivitis is an eye disease causing itching, redness, and tearing due to inflammatory mediator release. Thermoresponsive in situ gels, which undergo sol–gel transition at ocular surface temperature, are promising systems for prolonging residence time and improving therapeutic efficacy. This study aimed to develop and characterize

a novel thermosensitive in situ ocular gel containing hesperidin and hyaluronic acid (HA). Although hesperidin-loaded ocular in situ gels and HA-based mucoadhesive systems exist, to the best of our knowledge, no study has yet combined both in a single in situ gel formulation. Hesperidin, a flavonoid derived from citrus fruits with antioxidant and anti-inflammatory properties, was used in combination with HA, which provides mucoadhesive and moisturizing effects. Poloxamer 188 (P188) and poloxamer 407 (P407) were used as thermosensitive polymers. The formulations were prepared using the cold method. The Fourier transform infrared (FTIR) spectra of the gels with suitable sol–gel transition temperatures were obtained, and the gels were evaluated in terms of gelation time, pH, viscosity, mechanical properties and spreadability using Texture Analyser, and eye irritation potential using the HET-CAM assay.

Among the developed formulations, F2 (16% P407, 5% P188, 0.3% HA, 0.5% hesperidin, 5% PEG 400, 0.2% NaCl) and F9 (16% P407, 7% P188, 0.5% HA, 0.5% hesperidin, 5% PEG 400, 0.2% NaCl) were selected for characterization based on their suitable gelation temperatures (31.3±0.3 °C and 34.5±0.5 °C, respectively). FTIR analysis confirmed the compatibility of the components. Both formulations exhibited rapid gelation times (7.0±1.0 s for F2 and 8.7±0.6 s for F9), which are critical for effective ocular retention. The formulations demonstrated suitable pH values (approximately 6.8±0.02) and appropriate viscosity profiles at 4 and 32 °C (794.67±2.31 cP for F2 and 1764.33±3.51 cP for F9). Mechanical evaluations were performed at 4 °C and 32 °C, and at both temperatures, F2 demonstrated lower hardness (0.613±0.014 g at 32 °C), indicating easier spreadability with less applied force compared to F9. F2 also exhibited higher resilience (65.424±1.068% at 32 °C), suggesting better ability to tolerate applied stress, and superior springiness (97.472±0.550% at 32 °C), indicating improved elasticity. Spreadability studies were conducted at 4 °C and 32 °C, and at both temperatures, F2 exhibited lower firmness (45.62±0.16 g at 32 °C), work of shear (24.51±0.08 g·s at 32 °C), and work of adhesion (-11.05±0.12 g·s at 32 °C) compared to F9. These findings indicate that F2 provides easier application and better spreading behavior, suggesting greater suitability for patient use. Additionally, both formulations were evaluated for ocular irritation potential using the HET-CAM assay and were classified as non-irritant, as no hemorrhage, lysis, or coagulation was observed.

In conclusion, the developed hesperidin-loaded in situ gel formulations demonstrated suitable physicochemical, mechanical, and non-irritant properties for ocular application. Among them, formulation F2, with its shorter gelation time, lower hardness, higher spreadability, and improved elasticity and springiness, emerged as a promising candidate for a potential ophthalmic drug delivery system.

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PROMOTING AN INNOVATION FRIENDLY AND COMPETITIVE ENVIRONMENT IN THE NEW PHARMACEUTICAL LEGISLATION

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In April 2023 the European Commission adopted a proposal for a new pharmaceutical legislation to revise and replace the general pharmaceutical legislation in place over 20 years by now. The reform included two legislative proposals: a new Directive and a new Regulation providing the regulatory framework for all medicinal products.

More than two years after its release, in December 2025, a political agreement was reached by the Council and the European Parliament on the proposal.

The reform is a crucial step to ensure that high quality, safe and effective medicines are available for patients. It offers a modern, forward-looking, flexible and competitive framework by providing more support and improved conditions for innovation and investment, simplifying the regulatory environment, expanding availability and access of medicines across EU member states, safeguarding pharmaceutical supply chains, addressing medicines shortages, enabling timely market access for generic and biosimilar medicines, shifting towards digitalisation as well as enhancing environmental protection particularly addressing the environmental impact of medicinal products in line with the objective of the EU Green Deal and introducing measures against antimicrobial resistance as part of the One Health approach integrating human, animal and environmental health.

The presentation will focus on the new provisions, measures and conditions for research and development that the new legislation proposes for medicinal products including medicines for children and rare diseases. It will guide the audience through the reform: how it will promote innovation and competitiveness in a new, simplified and more efficient regulatory framework with an early regulatory and scientific support system, and by what means it will support more streamlined regulatory assessments, and how the regulatory and administrative burden will be reduced through simplified procedures. Furthermore the reform offers a more effective incentive framework for innovative medicines and priority antimicrobials and that research and development of new medicines should focus on patients' unmet needs and novel therapies.

Reference: Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency

Proposal for a DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the Union code relating to medicinal products for human use

GUM ARABIC AS A NOVEL FILM-FORMING BIOPOLYMER FOR LYSOZYME-LOADED BUCCAL DRUG DELIVERY SYSTEMS

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Among modern drug delivery systems, oral mucoadhesive formulations—particularly buccal films—represent a promising approach. These flexible dosage forms adhere to the oral mucosa for extended periods without causing discomfort, thereby facilitating the absorption of poorly permeable drugs. In addition, they can protect sensitive biomolecules such as peptides and proteins from degradation while enabling controlled drug release, potentially reducing dosing frequency. Buccal administration also offers the advantage of bypassing hepatic first-pass metabolism and a promising alternative route, enabling rapid onset of action, improved bioavailability, and enhanced patient compliance, particularly when combined with suitable mucoadhesive dosage forms. The presented study focuses on the development and characterization of gum arabic (GA)-based mucoadhesive buccal films as innovative carrier systems for protein delivery, using lyophilized egg white lysozyme as a model biopharmaceutical. The research is based on the well-known challenges associated with the oral administration of macromolecules, including enzymatic degradation, poor gastrointestinal stability, limited epithelial permeability, and extensive first-pass metabolism. Natural carbohydrate polymers have attracted significant interest in drug delivery due to their excellent safety, biocompatibility, and biodegradability

In this work, lysozyme-loaded GA films were prepared using a solvent casting technique and optimized through a 2^3 full factorial experimental design. Spray dried GA "Acacia Senegal" was used as a film-forming polymer. Propylene glycol was used as a plasticizer, citric acid was applied as a cross-linker. Sorbitol was involved as a conformation stabilizer polyol and sweetener. The prepared films were investigated with different methods as biological activity measurement, mechanical strength-mucoadhesivity test (self-developed texture analyzer), moisture content, water uptake, disintegration time, Raman and FT-IR spectroscopy, thermal analyses and drug release behavior. The results demonstrated that GA is a highly effective natural film-forming polymer with multifunctional properties. Importantly, the biological activity of lysozyme was largely preserved (86–93%) across the formulations, indicating that the GA matrix provides a stabilizing microenvironment capable of maintaining protein conformation during processing. Raman mapping confirmed the homogeneous distribution of lysozyme within the films.

Mechanical and physicochemical characterization showed that the films possess suitable properties for buccal application. The breaking hardness ranged between approximately 10–17 N, ensuring sufficient mechanical integrity during handling and application. The measured mucoadhesive forces indicate robust adhesion to mucosal

surfaces. Additionally, the short disintegration time facilitates rapid onset of drug release.

Thermal (DSC/TGA) and spectroscopic (FT-IR) analyses confirmed the absence of significant chemical interactions between components and demonstrated adequate thermal stability of the formulations.

Dissolution studies revealed a biphasic release pattern characterized by an initial burst release followed by a sustained release phase. This behavior is attributed to rapid hydration and swelling of the hydrophilic matrix.

Overall, this study provides the first systematic evaluation of gum arabic as a film-forming biopolymer for protein-loaded buccal delivery systems. The findings highlight its potential as a safe, biocompatible, and multifunctional excipient capable of stabilizing biopharmaceuticals and enabling controlled drug release. This work contributes to the advancement of natural polymer-based drug delivery technologies and supports the future development of innovative mucosal and potentially coating-related pharmaceutical systems.

DEVELOPMENT OF EXTRA-FINE INHALABLE VANCOMYCIN PARTICLES FOR TARGETED PULMONARY THERAPY

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Pulmonary infections remain a major therapeutic challenge, especially when conventional systemic treatments fail to achieve adequate drug concentrations at the site of infection [1]. This highlights the need for targeted pulmonary drug delivery approaches that can maximize local deposition while minimizing systemic exposure and associated side effects. Accordingly, the present study aimed to develop an extra-fine dry powder inhaler (DPI) formulation of vancomycin (VAN), a glycopeptide antibiotic commonly used to treat severe Gram-positive bacterial infections, such as methicillin-resistant Staphylococcus aureus infections.

The formulation was produced using nano spray drying (Büchi Nano Spray Dryer B90), a technique well-suited for generating particles in the respirable size range with controlled morphology [2]. To improve aerosolization performance and powder dispersibility, L-leucine (LEU) and D-mannitol (MAN) were incorporated as excipients. The following investigation methods were used to determine the characteristics of the formulation: laser diffraction, scanning electron microscopy (SEM), tap density tester, differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), Andersen Cascade Impactor (ACI), stochastic lung model, and A549 cell line test.

Particle size analysis revealed that the developed formulation exhibited a mean diameter of under 2 μm, which is considered extra-fine and optimal for deep lung deposition. The optimized formulation, composed of VAN:MAN:LEU in a 3:2:1 ratio, demonstrated spherical particle morphology and satisfactory flow properties, as indicated by a Hausner ratio of 1.25 and a Carr index of 19.99. Solid-state characterization techniques, including DSC and FTIR, confirmed the absence of significant physicochemical interactions between the active pharmaceutical ingredient and the excipients. Aerodynamic performance was evaluated using an *in vitro* method, demonstrating that the formulation achieved a mass median aerodynamic diameter (MMAD) of 2.37 μm and a fine particle fraction (FPF) of 79.72%. These results indicate excellent aerosolization efficiency and suggest superior performance compared to conventional or commercially available formulations. Furthermore, the in silico lung deposition test predicted efficient delivery of the particles to both bronchial and acinar regions, with an estimated deposition fraction of approximately 56–60%, highlighting the formulation's potential for effective deep lung targeting. Biocompatibility was assessed through *in vitro* cytotoxicity studies using alveolar epithelial cell lines, which confirmed that the formulation is well tolerated at relevant pulmonary concentrations.

In conclusion, the developed extra-fine vancomycin-loaded DPI formulation demonstrated promising physicochemical characteristics, aerodynamic performance, and favorable toxicity re-

sults. These findings support its potential as an effective platform for pulmonary antibiotic delivery. Nevertheless, further investigations, including long-term stability studies and *in vivo* efficacy evaluations, are necessary to fully establish its clinical applicability and therapeutic benefits.

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APPLICATION OF MICROFLUIDICS IN THE DEVELOPMENT OF OIL-IN-WATER EMULSIONS STABILIZED WITH SELECTED NATURAL GUMS

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Introduction: Growing concerns regarding the safety and environmental impact of synthetic surfactants have accelerated interest in natural polysaccharides as sustainable emulsion stabilizers. Droplet-based microfluidics offers precise, low-energy and material-efficient emulsification, enabling controlled formation of monodisperse droplets suitable for pharmaceutical and cosmetic formulations. The aim of this study was to evaluate the feasibility of microchannel emulsification for producing oil-in-water (O/W) emulsions stabilized with tragacanth gum (TG), guar gum (GG) or gum arabic (AG), and to relate droplet formation behavior to physicochemical properties of the continuous phases.

Materials and methods: Nine aqueous gum solutions (0.05–0.25% w/w) were prepared and characterized by surface tension and specific viscosity measurements. O/W emulsions (oil:water = 1:2) were generated using a custom 3D-printed flow-focusing microfluidic chip with controlled phase flow rates. Droplet formation and generation frequency were quantified by optical microscopy and video analysis. Correlations between gum concentration, physicochemical parameters and droplet frequency were assessed.

Results: Increasing gum concentration reduced surface tension and increased specific viscosity of the continuous phases. Stable oil droplet formation was achieved with TG and GG solutions across the investigated range, whereas AG failed to produce discrete droplets under identical conditions. Droplet generation frequency was higher for TG than GG and showed a strong positive correlation with gum concentration and a strong negative correlation with surface tension. These findings indicate that interfacial activity is the dominant factor governing droplet breakup in the applied microfluidic regime.

Conclusion: Flow-focusing microfluidic emulsification using low-concentration natural gums is a promising sustainable approach for producing O/W emulsions. Tragacanth and guar gums demonstrated effective stabilization in the 0.05–0.25% range, while gum arabic was ineffective under the tested conditions. The combination of natural polysaccharides and 3D-printed microfluidic devices represents a green and controllable platform for future pharmaceutical and cosmetic emulsion design.

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STATIC AND DYNAMIC SUPRAMOLECULAR MOLECULES FOR CANCER TREATMENT

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Calixarenes and related supramolecular macrocycles have emerged as versatile platforms in anticancer research, owing to their well-defined three-dimensional architectures, tunable functionalization, and ability to engage in host–guest interactions. These features enable both intrinsic biological activity and the design of advanced drug delivery systems. In parallel, cyclodextrins—another major class of macrocyclic hosts—have long

been recognized for their essential role in improving drug solubility and bioavailability. More recently, emerging families such as dynarenes are further expanding the scope of supramolecular chemistry toward precision oncology. This presentation will highlight the complementary contributions of calixarenes, cyclodextrins, and dynarene-type systems in combating cancer.

In oncology, applications of calixarenes span both direct anticancer activity and drug delivery. Several calixarene derivatives exhibit intrinsic cytotoxic or cytostatic effects through mechanisms such as enzyme inhibition, disruption of the cell cycle, and modulation of signaling pathways involved in tumor progression. In parallel, their ability to encapsulate therapeutic agents or form supramolecular assemblies enhances drug stability, solubility, and targeted delivery, positioning them as valuable scaffolds in nanomedicine.1 A notable example is OTX-008, a calixarene-based compound that acts as a selective inhibitor of galectin-1, a protein involved in tumor growth, angiogenesis, immune evasion, and metastasis. By targeting galectin-1, OTX-008 inhibits cancer cell proliferation, invasion, and tumor vascularization in preclinical models. Its progression into early-phase clinical trials underscores the translational potential of calixarene-based therapeutics.

Complementing calixarenes, cyclodextrins play a crucial and well-established role in pharmaceutical science. These cyclic oligosaccharides possess a hydrophobic cavity capable of forming inclusion complexes with poorly water-soluble drugs, thereby significantly enhancing their aqueous solubility and stability. In oncology, cyclodextrins are widely used to improve the formulation of chemotherapeutic agents, reduce systemic toxicity, and enable controlled release.3 Their biocompatibility and regulatory acceptance have made them indispensable tools for drug vectorization, including in clinically approved formulations.

In parallel, dynarenes—an emerging class of adaptive supramolecular receptors developed in our group—represent promising new opportunities in cancer therapy.[4] These compounds, generated through dynamic combinatorial chemistry, have recently been shown to exhibit cytostatic activity against cancer cell lines.

During this presentation, I will highlight our latest advances in the synthesis of these supramolecular systems generated through dynamic combinatorial chemistry and introduce the emergence of a new family of compounds -iminodithioines—which display particularly promising properties and open exciting perspectives for future anticancer applications.

In conclusion, we will see that the combined advances in calixarene-based therapeutics, the established role of cyclodextrins in drug solubilization and delivery, and the emerging potential of dynarenes highlight the growing impact of supramolecular chemistry in cancer treatment (NextNano4Cancer ERA4HEALPH project).

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TESTING ANTIMICROBIAL ACTIVITY OF ELECTROSPUN NANOFIBERS: FROM STANDARD ASSAYS (KEYNOTE)

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Chronic non-healing wounds represent a growing socioeconomic burden, creating an urgent need for innovative strategies to improve healing outcomes. Antimicrobial electrospun wound dressings are a promising approach, offering targeted antimicrobial delivery and the potential to enhance wound healing.

To evaluate the antibacterial performance of electrospun drug delivery systems loaded with antimicrobials or antibiotics, standard antimicrobial activity assays are often applied. While these methods support reproducibility and comparability, they lack biological relevance, relying on simplified conditions that poorly reflect the complexity of the wound environment. This limitation is particularly evident in biofilm research despite the well-recognized role of biofilms in chronic wounds. To address these gaps, different *in vitro* and *ex vivo* antibacterial activity testing methods have been developed.

Herein, different approaches for assessing antimicrobial activity are outlined, tracing progression from standard assays to biorelevant *ex vivo* biofilm models.

Key lessons learned are discussed with respect to method selection, model design, and data interpretation, illustrating how testing strategy strongly influences conclusions about antimicrobial efficacy. These insights support more meaningful evaluation and rational design of electrospun antimicrobial wound dressings, while contributing to ethically aligned research strategies that reduce reliance on animal testing.

CNS-SELECTIVE ESTROGEN DELIVERY VIA THE DHED PRODRUG: TARGETING NEUROLOGICAL, PSYCHIATRIC, AND NEURODEGENERATIVE DISEASES (KEYNOTE)

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17β-Estradiol (E2), the primary and most potent form of human estrogen, has long been recognized for its wide-ranging biological actions throughout the body. Beyond its well-established functions in reproductive physiology, E2 exerts significant influence within the central nervous system (CNS) where it plays a critical role in maintaining both brain and eye health in a sex-dependent manner, influencing neuronal survival, synaptic plasticity, and cognitive function in a sex-dependent manner.

A decline in E2 levels, whether natural or iatrogenic, has been associated with an elevated risk of neurological and psychiatric conditions affecting the brain, including Alzheimer's disease, Parkinson's disease, depression, and anxiety. The retina, as part of the CNS, is similarly vulnerable, with hypoestrogenicity linked to increased risk of glaucoma, age-related macular degeneration, and heightened susceptibility to retinal cell death leading to vision impairment or loss. Despite this recognized need for "estrogenic" CNS, current estrogen replacement therapies present a significant clinical challenge: systemic hormone administration leads to serious side effects, including stimulation of uterine tissue, promotion of hormone-sensitive tumor growth, feminization in males, and cardiovascular liability—limiting their viability as therapeutic options for neurological, psychiatric, and broader neuroprotective indications.

Here, we present a strategy centered on the development of a small-molecule bioprecursor prodrug 10β,17β-dihydroxyestra-1,4-dien-3-one (DHED). DHED is biologically inert upon systemic administration but undergoes selective conversion to E2 within CNS tissues, allowing the brain and retina to receive estrogen signaling while peripheral organs remain unexposed to the hormone.

CNS-selective E2 production from DHED has been demonstrated through bioanalytical assays and efficacy studies across multiple preclinical animal models of estrogen-responsive neurological and retinal disease. Complementing these studies, mass spectrometry-based proteomics has been employed to gain deeper insight into the neurodegenerative processes underlying these conditions and the mechanistic basis of their remedy by the DHED approach. These investigations encompass both chronic systemic and topical delivery routes, with consistent evidence that peripheral hormonal exposure is effectively eliminated in sex-independent manner.

Taken together, preclinical data presented here support DHED as a promising approach to CNS-targeted estrogen therapy with potential for safe and efficacious treatment of neurodegeneration, as well as neurological and psychiatric consequences of estrogen deficiency.

Keywords: 17β-Estradiol; DHED; Brain; Retina; Proteomics

PRECLINICAL CHARACTERIZATION OF NOVEL ANTIMICROBIAL MATERIALS FROM LABORATORY TO LIVING SYSTEMS (KEYNOTE)

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Chronic wound infections remain one of the most persistent and costly challenges in modern medicine, yet the preclinical tools used to study them often fall short of reflecting the complex biological reality clinicians face. Our group has developed chronic wound infection models and tested how these enable meaningful evaluation of innovative antimicrobial materials, with a particular focus on electrospun fiber-based dressings. I will introduce our recent work on *in vivo* wound infection model development, its challenges, and opportunities. By integrating comorbidities, controlled biofilm-based inoculation, and diverse wound types, this model

enables a more accurate assessment of infection dynamics and wound healing processes. Such models provide a good platform for testing novel antimicrobial materials, like electrospun fiber dressings. Together, these approaches illustrate how improved wound infection models in preclinical characterization can accelerate the development of effective therapies and bring next-generation wound treatments closer to clinical translation.

DEVELOPMENT AND CHARACTERIZATION OF IVERMECTIN-LOADED MICROEMULSION-BASED TOPICAL GEL FORMULATIONS

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Ivermectin (IVM) is a potent agent widely utilized in dermatological applications due to its multifaceted anti-inflammatory and anti-parasitic properties [1]. However, its therapeutic potential is often hindered by its highly lipophilic nature, which leads to poor aqueous solubility and limited skin penetration [2]. Traditional topical formulations often struggle to overcome the skin's natural barrier, resulting in low bioavailability at the target site [2]. To address these limitations, this study focuses on the development and optimization of ivermectin-loaded microemulsion-based topical gel formulations. These advanced delivery systems are designed to improve the solubility of the drug and enhance its transport through the stratum corneum, ensuring controlled release and increased therapeutic efficacy for the management of skin disorders.

Ivermectin-loaded microemulsions were developed by constructing ternary phase diagrams via the titration method using a mixture of selected oils, surfactants, and co-surfactants [3]. To improve the residence time on the skin, the viscosity of these systems was increased by incorporating a polymer to form microemulsion-based gels [4]. The resulting formulations were characterized based on their droplet size, zeta potential, polydispersity index, rheological properties, *in vitro* drug release profiles and *in vivo* dermal irritation.

The developed microemulsions exhibited droplet sizes ranging from 10 to 200 nm and demonstrated high thermodynamic stability. The addition of the polymer significantly enhanced the viscosity, providing ideal rheological properties for topical application. *In vitro* release studies indicated that IVM was released from the microemulsion system in a controlled manner, with improved skin penetration compared to traditional formulations. Furthermore, the formulations were found to be non-irritating in *in vivo* dermal irritation tests, confirming their safety and suitability for topical use.

This study demonstrates that IVM-loaded microemulsion-based gel systems are a promising carrier platform for for topical drug delivery. By improving the solubility and topical bioavailability of lipophilic drugs, this innovative approach has the potential to significantly improve patient compliance and clinical outcomes.

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IN VITRO + *IN SILICO*: ADVANCED TOOLS FOR ORAL ABSORPTION PREDICTION

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A large fraction of chemical entities entering original or generic development fall into BCS Class II or IV, where low solubility and dissolution rate often limit oral bioavailability. To overcome these barriers, advanced formulation strategies such as amorphous solid dispersions, lipid-based delivery systems, and nanonization have become well-established approaches to increase apparent solubility and enhance absorption; however, they also introduce new complexities.

To characterize and optimize these advanced

formulations, dissolution-permeation (also called flux) devices are widely used in pre-formulation and formulation development enabling simultaneous assessment of dissolution and permeation across a membrane, thereby providing insight into both drug release and absorption potential. While these measurement systems can capture complicated interactions like the solubility-permeability interplay, the flat membrane structure and the relatively small surface area to volume ratio pose challenges to accurately capture all aspect of absorption. However, by combining experimental flux results with physiologically relevant mechanistic modelling, it is possible to identify the rate-limiting steps of absorption, account for the particle drift of colloidal species and nanoparticles, or in general bridge the gap between *in vitro* measurements and *in vivo* pharmacokinetics that allows quantitative prediction of absorption rates across preclinical species and humans.

In the presentation, 3 case studies are discussed. The first one demonstrated how mechanistic modelling is essential to understand the impact of small particles on absorption. By running multiple dissolution-permeation assays at various dose levels, it is possible to characterise the behaviour of the celecoxib particles in the unstirred water layer. This information can then be scaled up to the *in vivo* environment, and the accurate impact of particle drifting can be captured.

The second case study introduced a comparison of piroxicam nano vs micronized formulations applied in low and high doses, and also assessed the rate-limiting step of absorption based on the Fraction absorbed Classification System (FaCS).Based on the modelling results, the absorption at low dosing conditions was dissolution rate-limited, while at high doses, the absorption was rate-limited by solubility for both formulations, and the absorption advantage of the nano formulation was coming from the difference in solubilities caused by the different crystal forms. In all cases, the predicted *in vivo* absorption rate was in good agreement with the human and rat *in vivo* PK profile.

The third case study showed a comparison of different formulation strategies. An amorphous solid dispersion was compared to a nanocrystalline formulation. Based on the *in vitro* dissolution-permeation data the ASD seemed to outperform the nanocrystalline formulation, but when the particle drifting was considered by the modelling the formulations turned out to be bioequivalent, which was confirmed by *in vivo* human studies as well.

To summarise, the case studies demonstrate that combined *in vitro* flux assay and mechanistic modelling enhances formulation selection, reduces development risk, and accelerates the path toward clinical evaluation.

CONTROLLING THE DRUG RELEASE AND PERMEATION PROFILE OF NASAL POLYMERIC MICELLES: FEASIBILITY STUDIES

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Nasal drug delivery offers a variety of advantages, including the bypass of the first-pass effect, increasing the bioavailability of drugs. This phenomenon can also be extended to the benefits of polymeric nanoparticles, including the self-assembling structures of polymeric micelles, which can encapsulate active substances with poor water solubility and permeability. Challenges, however, surround the administration of nanoparticles via nasal drug delivery, including controlling drug release and the permeation of these rapidly permeating particles. In this presentation, the aim was to demonstrate various formulation studies targeting different segments of nasal drug administration, including the development of systems that rapidly deliver drugs to the central nervous system or, conversely, prolong the residence of nanoparticles in the nasal cavity.

The methodology of the studies varied based on the systems' unique characteristics. Common studies included colloidal characterization via dynamic light scattering and determination of thermodynamic solubility and related parameters. *In vitro* nasal dosage form studies included the determination of mucoadhesion, drug release, and permeation under at least one *in vitro* condition. To demonstrate the applicability of rapidly permeating polymeric micelles, dexamethasone-loaded polymeric micelles were first developed with a particle size of approximately 100 nm and a monodisperse size distribution. The particles provided rapid absorption into the central nervous system, as demonstrated in *in vivo* studies. *In vivo* brain distribution studies also confirmed that a higher percentage of drugs is located in the olfactory bulb, thereby demonstrating the feasibility of a direct nose-to-brain drug delivery route. Similarly, meloxicam-loaded polymeric micelles were also

evaluated *in vivo*, and are capable of direct nose-to-brain delivery. Citalopram, an antidepressant model drug, was loaded into thermosensitive polymeric micelles, which exhibited more than 90% drug release within 15 minutes due to a change in micellar structure induced by their thermosensitivity. These phenomena can be explained by the small particle size (80–120 nm) and the incorporation of penetration-enhancing polymers into the micellar structure. On the contrary, hyaluronic acid-modified vinpocetine-loaded polymeric micelles were also formulated via nanospray-drying to demonstrate increased residence time in the nasal cavity. This delivery strategy is also of paramount importance, as increasing the likelihood and durability of permeation is just as important as ensuring that most of the drug permeates across the nasal mucosa within 15 – 30 minutes. There was a clear correlation between the concentration and molecular weight of the added hyaluronic acid, which clearly directs the possible delivery route of the nanoparticles.

A similar principle was also established for risperidone-loaded polymeric micelles, which were embedded in the ion-sensitive gellan gum excipient, thereby leading to a concentration-dependent change in the sustained-release profile of the drugs. In conclusion, nasal drug delivery can be programmed and modified with a clear research design that focuses on the therapeutic needs that are viable via nasal drug delivery, alongside the proper selection of micelle-forming polymers.

INVESTIGATION OF THE EFFECTIVENESS OF PIGMENTS FOR PROTECTION OF PHOTOSENSITIVE DRUGS DURING LASER MARKING OF SOLID DOSAGE FORMS

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Introduction: Laser marking is of emerging interest in the pharmaceutical industry to enable fast labelling of personalized medicines or for anti-counterfeiting purposes. However, to the best of our knowledge, no study investigated their effect if the labelled tablet contains photosensitive drug. Objectives: Therefore, the aim of current study was to evaluate the photoprotective effect of various opacifiers on nifedipine tablets during marking with various lasers such as Ti:Sa laser (781 nm), Nd:YAG laser (532 nm), KrF excimer laser (248 nm) and ArF excimer laser (193 nm), against dark stored samples as negative- and sunlight exposed tablets as positive control. Materials and methods: Various TF coating formulations (talc, $CaCO_3$, ZnO, and Fe_3O_4) were manufactured, with a reference (TiO_2) for comparison. All formulations were stored under the same conditions and then exposed to sunlight (6 months) or short-term laser ablation at different wavelengths (193 nm, 248 nm, 532 nm, and 781 nm). The photostability of these formulations was evaluated using Raman microscopy and high-performance liquid chromatography (HPLC) measurements.

Results and discussion: Although the EU has maintained the use of TiO_2 in medicines, it has recommended an ongoing search for suitable alternatives. The current study demonstrated the feasibility of the replacement of TiO_2 in coatings with different alternatives (talc, $CaCO_3$, ZnO and Fe_3O_4) to achieve complete coverage and optimal photoprotection of nifedipine tablets from sunlight exposure and from laser treatment.

The titanium containing and titanium free coating formulations exhibited similar properties and the color stability of the coatings is not affected by the applied treatments, although minor color changes were observed for uncoated, pigment free, talc and $CaCO_3$ containing formulations after exposure to sunlight, which was probably due to the photodegradation of the drug. On the other hand, the formulations containing TiO_2, ZnO, Fe_3O_4 and the Opadry Brown coated tablets maintained their color throughout the study period, and overall formulations containing TiO_2 and/or black iron oxide were able to suitably protect nifedipine containing tablets for at least 4 months from direct sunlight exposure. Nevertheless, more specific results were associated with laser treatments. Ti:Sa laser was found to be the safest and did not affect the appearance of any of the coatings applied and most of the pigments were able to protect the core from the destructive effect despite the complete ablation of the coating layer. In contrast, Nd:YAG laser was the most destructive and only Fe_3O_4 exhibited suitable protection

against it. TiO_2 and ZnO-containing coatings exhibited a small colored ring around the ablation region after treatment with UV lasers, which is related to the effective UV absorption of these materials in this wavelength region, which was in good accordance with their good protective effect against these types of lasers.

Conclusion: Overall, it can be stated that laser marking of tablets containing photosensitive materials may be done safely, but considerable care must be taken to select the appropriate combination of the applied type of laser and photoprotective pigments.

INKJET PRINTING IN PERSONALISED DRUG DELIVERY: INK FORMULATION STABILITY IMPROVEMENT VIA A DRY PRE FORMULATION APPROACH

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Advanced pharmaceutical printing technologies are emerging as a powerful platform for personalized drug delivery, enabling the preparation of dosage forms tailored to individual patients in terms of dose, drug combination, and release profile. Among these approaches, inkjet printing has attracted particular attention due to its high precision, low material consumption, non-contact deposition, and compatibility with temperature-sensitive substrates (especially in piezoelectric systems). As a versatile 2D printing technique, and by some authors also considered as one of 3D printing techniques, inkjet printing has been widely investigated for the deposition of active pharmaceutical ingredients (APIs) onto edible films and other biocompatible substrates, as well as onto transdermal systems, microneedle arrays, and implantable or diagnostic surfaces (1). Its key advantages include accurate microdosing, spatially controlled drug placement, rapid prototyping, scalability for small-batch production, and suitability for on-demand manufacturing in hospital and pharmacy settings. Pharmaceutical ink formulations for inkjet printing can range from drug solutions to colloidal systems and particle dispersions, including micro- and nanoparticle-based inks. While particulate inks offer important advantages, such as improved solubilisation of poorly water-soluble drugs, protection of labile APIs, and greater formulation flexibility, they also introduce challenges related to colloidal stability, sedimentation or aggregation, and printhead compatibility (2). More broadly, inkjet printing requires tight control over ink properties (e.g., viscosity, surface tension, and particle size distribution), and performance can be compromised by droplet instability, dose variability, and nozzle clogging, particularly when particle-based inks are used. In addition, the long-term chemical and physical stability of both drug-containing solutions used as inks and particle-based drug-containing inks remains a major limitation, as many APIs are susceptible to hydrolytic, oxidative, or photolytic degradation during storage, while suspended particles tend to aggregate or sediment.

Our solution to the challenge of physical and chemical instability of the final ink formulation is to prepare the ink formulation right before its use (*ex tempore*) by simply adding the ink base medium to prepared drug-loaded particles, which can be achieved with appropriate pre-formulation of non-volatile ink constituents. In this concept, the drug is stored in a dry, more stable intermediate form and converted into a printable ink only immediately before use, thereby reducing exposure to destabilising liquid environments, extending shelf life, and improving formulation robustness. In our work, this dry intermediate is prepared as spray-dried drug-loaded micro- and nanoparticles obtained from optimised emulsions, which can be rapidly redispersed into a suitable printing medium prior to printing (3). Beyond improved stability, this approach also provides formulation flexibility, supports dose individualisation, and may facilitate the handling of poorly water-soluble or otherwise labile compounds.

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AI-BASED PREDICTION AND PREVENTION OF DRUG ADVERSE EFFECTS BY REAL WORLD DATA: FOCUS ON ANTICOAGULATION

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Major bleeding is a serious adverse drug event (ADE) of anticoagulation therapy (heparins, vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs)), and thus anticoagulants are classified as high-risk drugs. The majority of the anticoagulation-associated ADEs, i.e. bleeding events, could be prevented.

The general objective of the study is to identify risk factor profiles for major bleeding in anticoagulated patients by using up-to-date real-world data and to develop an AI-based risk prediction model to support the prevention of ADEs and safe prescribing in clinical practice. Together with a digital health twin approach, machine learning will be employed, which has potential to surpass current cumulative risk scoring systems.

The specific objectives are: 1) To identify risk factor profiles leading to major bleeding events in a comprehensive real-world data set with approximately 460 000 patients and their full medical history 2) To determine the importance of major bleeding risk factors for each anticoagulant, including dose and drug-drug interactions 3) To detect possible novel, unidentified risk factors using advanced feature selection techniques and 4) To develop AI-based risk prediction model (digital health twin) to support safe anticoagulation therapy and prevention of major bleedings and validate it with two external datasets . The approach can also be applied to other classes of drugs.

The study data comprised all the adult Finnish patients with venous thromboembolism (VTE) or atrial fibrillation (AF) who have had at least one anticoagulation therapy prescription (VKA, DOAC or heparin) through study period 2015-2023. The data is gathered from national data controllers: The Social Insurance Institution of Finland, Finnish Institute for Health and Welfare, and Statistics Finland.

DEVELOPMENT AND EVALUATION OF ALLANTOIN-CONTAINING HYDROGEL FORMULATIONS FOR SCAR TREATMENT

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Introduction: Millions of people worldwide are affected by various types of scars. Topical treatments are preferred for scars due to their non-invasive nature and ease of application(1,2). Allantoin, known for its cell-regenerating and moisturizing effects, is frequently used alone or in combination for scar treatment. Hydrogels, which provide high biocompatibility and controlled release, are one of the dosage forms that accelerate the wound healing process(3,4).

Objectives: The aim of our study is the development and characterization of allantoin-containing hydrogel formulations for topical scar treatment.

Methods: Allantoin was generously provided by Santa Farma, İlaç (Turkey) and polymers were generously provided by Ashland, USA. PEG200® were purchased from J.T.Baker (Phillipsburg,USA). A spectrophotometric method was developed for allantoin in gel formulation and validated according to the ICH guideline. Studies were performed in pH 7.4 phosphate buffer solution (PBS) at 210 nm. Gel formulations were prepared using various cellulose derivatives and different methods, and based on the results obtained, it was decided to continue the studies with hydroxyethyl cellulose (Natrosol). Allantoin-free gels were prepared using Natrosol by dissolving it in water at room temperature at concentrations of 1 to 4% (w/v). The most suitable formulation was determined to be the method prepared by dissolving 1% (w/w) Allantoin in an aqueous solution containing 39% (v/v) PEG200 at 50°C, followed by the addition of 1% (w/v) Natrosol. The pH of all gels was measured using pH strip (ISOLAB). The viscosities of gels were measured using a Brookfield DV-III cone-plate viscometer at specified shear rates (0.02–200 s^{-1}) and at a temperature of 25±0.5 °C with a CP-52 spindle (n = 3). Drug release studies were performed to compare the al-

lantoin suspension and allantoin-containing Natrosol-based gel formulations using Franz diffusion cells with a cellulose membrane (MWCO:12-14 kDa) at 32 ± 0.5°C for 6 hours (n=6). A pH 7.4 PBS was used as the receptor medium.

Results and Discussion: Clear, homogeneous and transparent gels with suitable viscosity for topical application were obtained. The pH of the Natrosol-based gel formulation containing allantoin was found to be 4.5, which was observed to be suitable for skin pH. The Natrosol-based gel formulation containing allantoin had a viscosity of 1441 cP at a shear rate of 40 s^{-1} and exhibited pseudoplastic flow. After 6 hours, the Natrosol-based gel formulation exhibited a significantly higher allantoin release of 92.2±27.9% compared to 68.4±55.7% from the suspension, with corresponding permeability coefficients determined as 0.0098±0.0048 $cm.h^{-1}$ and 0.0021±0.0014 $cm.h^{-1}$, respectively.

Conclusion: A Natrosol-based hydrogel with suitable pH, viscosity, and release properties for the topical application of allantoin was successfully developed for scar treatment. In the continuation of this study, it is planned to conduct cell culture studies in fibroblast cells with the developed optimum gel formulation.

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NANOFIBROUS DRUG DELIVERY SYSTEMS: FROM LOCAL ANTIBACTERIAL THERAPY TO ORODISPERSIBLE FORMULATIONS

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Fibrous systems enable the rational design of dosage forms tailored to markedly different therapeutic needs by the appropriate selection of the polymer matrix and formulation strategy.

The present work demonstrates the flexibility of electrospun nanofibers through two distinct application-oriented approaches: local antibacterial therapy and fast-dissolving orodispersible drug delivery.

In the first part of the study, polycaprolactone (PCL)-based nanofibers were developed as local drug delivery systems for the treatment of external bacterial infections. Local therapy is advantageous in reducing systemic side effects and mitigating the development of antibiotic resistance. Antibiotics with different physicochemical properties, including amoxicillin, ciprofloxacin, and chloramphenicol, were dispersed in PCL solutions using suitable solvent systems and processed by electrospinning. The resulting nanofibers were characterized by scanning electron microscopy to assess morphology and fiber diameter. Solid-state characterization was performed using X-ray powder diffraction, while drug release was evaluated by high-performance liquid chromatography with UV detection. The results confirmed the successful formation of nanofibrous structures with diameters in the nanometer range. XRPD analysis revealed that the incorporated antibiotics were present in an amorphous form or as molecular solid dispersions within the fibers. Drug release exceeded 80% for all three antibiotics, indicating favorable release characteristics. In addition, improved stability was observed for amoxicillin, while enhanced apparent solubility was achieved for ciprofloxacin.

In the second part, hydrophilic poly(vinyl pyrrolidone) (PVP) nanofibers were developed as orodispersible formulations to improve patient compliance, particularly for individuals with swallowing difficulties. The salt form of diclofenac and a highly water-soluble polymer matrix were selected to promote rapid disintegration and immediate drug release in the oral cavity. It is well established that the molecular weight and concentration of the polymer influence the success of the electrospinning process. Therefore, to optimize the applied method, the effects of these parameters were systematically investigated. Electrospinning solutions with three different polymer concentrations were prepared from five PVP grades of different molecular weights. The collected samples were examined by scanning electron microscopy, which allowed the definition of the viscosity range required to obtain the desired fiber morphology. Following carrier optimization, diclofenac-loaded nanofibrous films were produced

using double-needle electrospinning, facilitated by a custom-designed 3D-printed needle holder. The formulations were characterized in terms of morphology, solid-state properties, disintegration behavior, dissolution performance, biocompatibility, and stability. The nanofibers exhibited rapid disintegration - approximately 5 s in artificial saliva and around 41 s on an artificial tongue model - and immediate drug release, with complete dissolution achieved within 10 minutes. Biocompatibility studies confirmed good tolerability, and stability testing demonstrated physical and chemical stability over six months.

Overall, these results highlight electrospun nanofibers as a highly adaptable drug delivery platform, capable of addressing diverse therapeutic challenges ranging from localized antibacterial treatment to fast-acting orodispersible dosage forms through formulation-driven design.

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DESIGN AND EVALUATION OF LYOPHILIZED CURCUMIN-LOADED MUCOADHESIVE BUCCAL WAFERS CONTAINING DEEP EUTECTIC SOLVENT VIA DESIGN OF EXPERIMENTS

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Curcumin, a polyphenol extracted from Curcuma longa, has antioxidant, antimicrobial, anti-inflammatory, and wound-healing properties. However, its pharmaceutical use is limited due to poor aqueous solubility and low bioavailability. Deep eutectic solvents have recently gained attention as promising systems to improve drug solubility, stability, and formulation performance. Buccal wafers are porous, sponge-like dosage forms prepared by lyophilization and may provide rapid hydration, mucoadhesion, and prolonged residence time on the oral mucosa. This study aimed to develop curcumin-loaded buccal wafers containing deep eutectic solvent for local treatment of oral mucosal diseases.

The solubility of curcumin in different deep eutectic solvents at 25 °C was determined in a previous study. The optimal deep eutectic solvent was selected based on viscosity, pH, organoleptic properties, and curcumin solubility. Choline chloride:Propylene glycol at a 1:4 molar ratio was used as the selected solvent system. Curcumin-loaded buccal wafers were prepared by lyophilization using HPMC K100 in combination with chitosan or pectin as mucoadhesive polymers. A Central Composite Design was applied to optimize the formulation variables. Mucoadhesive strength, swelling index, and swelling duration were evaluated as response parameters. Optimized wafers were further characterized in terms of weight, thickness, pH, mechanical properties, FTIR analysis, *in vitro* drug release, ex vivo permeation, and cell culture studies.

The selected deep eutectic solvent increased the solubility of curcumin and showed suitable properties for pharmaceutical formulation. According to the experimental design results, optimized chitosan- and pectin-containing buccal wafer formulations were selected. The wafers showed suitable mucoadhesive properties, controlled swelling behavior, and acceptable mechanical characteristics. *In vitro* release studies demonstrated sustained curcumin release. Ex vivo permeation remained limited, supporting the local effect of the formulation on the buccal mucosa. Cell culture studies showed good cytocompatibility, antioxidant and anti-inflammatory activity, and wound-healing potential.

In conclusion, curcumin-loaded buccal wafers containing deep eutectic solvent were successfully developed and optimized. These formulations may be considered promising local drug delivery systems for oral mucosal diseases. The use of deep eutectic solvent improved the formulation potential of poorly water-soluble curcumin, while the lyophilized wafer structure provided suitable mucoadhesive and swelling properties for buccal application.

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Key words: Curcumin, Buccal wafer, Deep eutectic solvent, solubility, curcumin-loaded

CALCIUM BUTYRATE LOADED HYDROGELS FOR ENHANCED TOPICAL TREATMENT OF SKIN DISORDERS

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Butyric acid is one of the short fatty acids composed of four carbon atoms. It offers various biological effects, such as serving as an energy source for intestinal epithelial cells, supporting colonic barrier function, and exhibiting antioxidant and anti-inflammatory activity. Because of volatility and inactivation in the gastric environment, it is required to approach utilizing the calcium salt of butyric acid. This study aimed to formulate calcium butyrate (CAB) containing sodium alginate and carboxymethylcellulose (CMC)-based hydrogels and evaluate their efficiency on topical remedies for local inflammatory diseases. For this purpose, comparative studies were carried out with and without CAB. The formulations with different concentrations of sodium alginate and CMC were subjected to characterization studies.

The formulations' pH values were measured by immersing a digital pH meter, and the results were between 7.15±0.05 and 7.87±0.08, and an inference was made that the gels were biocompatible for biological tissues. FTIR analysis was performed not only on the formulations but also on all the ingredients of the formulations individually. The spectra displayed a slight difference after adding CAB into the blank formulations, which is attributed to crosslinking of polymers with Ca^{2+} ions of CAB, as well as weak hydrogen bonds or ionic interactions between CAB and the polymer matrix. Ca^{2+} ions strengthen the polymer network structure, increase the structural stability of the gels, decrease the swelling capacity of the hydrogel, and consequently, controlled release of CAB. Additionally, chemical compatibility was kept with no degradation. Viscosity of the gels was measured with a Brookfield viscometer at room temperature, and the results were found between 3638±157.82 and 10300±167.03 cP, which was considered suitable fluidity for both remaining on the local biological surface and spilling out of the packaging container. Also, the spreadability of the gels was analyzed with the help of a Texture Profile Analyzer through the spreadability mode in terms of firmness, work of shear, stickiness and work of adhesion parameters. The results suggested that loading of CAB brought to the blank formulations higher firmness and molecular interactions resulting in adhesion to external materials, including biological tissues. Moreover, antimicrobial activity was assessed against *Staphylococcus aureus* (ATCC 6538), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 8739), and *Candida albicans* (ATCC 10231) by Agar Well diffusion method. The conducted test with the most common skin-related pathogen microorganisms revealed that CAB-loaded hydrogels exhibited an effective inhibition zone over *S. aureus*, *E. coli*, and *C. albicans*. Overall, CAB containing hydrogels are proven to be a suitable antimicrobial and anti-inflammatory cure alternative, and open to further *in vivo* studies.

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NEW OINDPS GUIDELINE: REALITY VS. REGULATORY EXPECTATIOS

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Orally Inhaled Drug Products (OIDPs) represent a new category of product that are rather complicated from the regulatory point of view. These are pharmaceutical dosage forms, where therapeutic performance is determined not only by formulation characteristics, but also by device design, patient's use. There is an intricate interplay between aerosol performance and regional drug deposition. Among OIDPs, dry powder inhalers (DPIs) pose particular regulatory challenges, because even small differences in particle engineering, manufacturing processes, inhaler resistance, excipient composition, or device architecture may create significant difference in clinical performance. Consequently, establishing therapeutic equivalence in generic OIDPs is a complicated work, which requires a multidisciplinary scientific

strategy that extends well beyond conventional pharmaceutical equivalence.

Regulatory expectations for these complicated products is evolving. The U.S. Food and Drug Administration (FDA) has established highly "product-specific" regulatory pathways and, for many inhalation products, requires clinical studies or comprehensive *in vitro* and *in vivo* correlation evidence.

In contrast, the European Medicines Agency (EMA) provides a broader scientific framework, whereby the agency relays most key regulatory decisions subject to scientific interpretation to national authorities. Although this approach may seem to allow flexibility at the national level, it also creates a multitude of interpretations, and inconsistencies in regulatory perspective. The end results is uncertainty for developers of generic inhalation products.

As increasingly sophisticated inhaled medicines reach the market, greater international harmonization and more detailed scientific guidance become essential. In this context, the paper consists of three streams of argument. Firstly, using DPIs as representative examples, the lecture will examine critical regulatory challenges including device comparability, Q1/Q2 differences, regulatory significance of functional excipients (i.e. magnesium stearate). Secondly, the lecture examines problems in reference product/device selection, inhaler resistance classification. The lecture also points out limitations of standardized *in vitro* performance testing. Thirdly and finally, the lecture will propose perspectives for prospective harmonization of regulatory strategies, focusing the underpinning need for detailed, product-specific guidance.

The paper emphasizes the challenges that emerging technologies pose for regulatory science, such as advanced aerodynamic characterization, physiologically based in silico modelling, computational fluid dynamics, reliance on AI, digital twins, and integrated weight-of-evidence approaches. These technologies improve the prediction of clinical performance, while reducing the overreliance on comparative clinical endpoint studies.

In order to support the development of complicated generics, the paper argues, we need prospective strategies similar to those of FDA.

The paper underlines new developments that should be incorporated into next-generation regulatory guidance, such as standardized *in vitro* methodologies, clinically relevant in silico models, mechanistic evidence frameworks, and globally harmonized terminology and criteria.

Next generation regulatory science should move beyond a predominantly clinical evidence-driven paradigm toward a mechanistic evidence-driven framework. Advanced *in vitro* methodologies, in silico modelling, artificial intelligence, and integrated scientific evidence collectively reduce regulatory uncertainty and overhaul, while minimizing unnecessary clinical studies. Ultimately, the goal must be acceleration of patient access to high-quality generic topical and inhaled medicines without compromising safety or therapeutic efficacy.

DESIGN AND OPTIMIZATION OF TALAZOPARIB-LOADED THERMOSENSITIVE RHAMNOSOMES FOR METASTATIC BREAST CANCER THERAPY

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Introduction: Breast cancer is a leading malignancy worldwide, yet the treatment of peritoneal metastasis remains unclear. While chemotherapeutics are widely used, drug resistance limits their efficacy. Hyperthermia enhances anticancer activity, and talazoparib (TLZ), a PARP inhibitor, induces cancer cell death by inhibiting DNA repair. Liposomes are effective drug carriers, and rhamnolipids have been shown to enhance anticancer effects. In this study, thermosensitive rhamnolipid-containing liposomes (rhamnosomes) were developed for improved intracellular delivery and temperature-triggered release. The effects of TLZ-loaded rhamnosomes on cytotoxicity, cellular uptake, and apoptosis were evaluated in TNBC 4T1 cells.

Methods: Optimization of Prepared Rhamnosomes

TLZ-loaded rhamnosomes were prepared by thin-film hydration of DPPC/DSPE-PEG2000/rhamnolipid/cholesterol, followed by sonication. Liposomes were purified by centrifugation, then frozen at −80°C and lyophilized for 24 h.

A Central Composite Design (CCD) was used to optimize PPC/cholesterol/DSPE-PEG2000/ rhamnolipid liposomes, with DSPE-PEG2000 fixed at 5% and other lipid ratios varied. Particle size, PDI, zeta potential, drug loading efficiency, and phase transition temperature were evaluated, and data were analyzed using Design-Expert software (Stat-Ease Inc., USA).

In Vitro Release Studies: Drug release was assessed by the dialysis bag method, where TLZ or TLZ-loaded liposomes (0.5 mg) were placed in dialysis bags (12–14 kDa) and incubated in pH 7.4 buffer at 37°C, 39°C, and 41°C under stirring. Samples were collected at set intervals and analyzed by HPLC.

MTT Assay, Cellular Uptake of Rhamnosome and Cell Death Analysis

4T1 cells were treated with free or TLZ-loaded formulations (24, 48, 72 h), and temperature-dependent effects were assessed at 37°C, 39°C, and 41°C. 4T1 cells were treated with formulations for 1,2 and 4h, followed by washing, lysis, and HPLC quantification of TLZ. Cell death was assessed by Annexin V-FITC/PI staining and flow cytometry (Esim et al., 2024).

Results and discussion: Characterization of Optimum Formulation

Design-Expert software (Stat-Ease Inc., USA) was used to analyze variable effects, yielding significant polynomial models. Response surface plots illustrated interactions, and DPPC-containing liposomes were successfully prepared with appropriate phase transition temperatures.

In vitro Release Studies: Liposomes containing >50% DPPC showed increased release at 41°C, while rhamnolipid enhanced release even at low DPPC levels (particularly at 39–41°C); free talazoparib exhibited no temperature-dependent behavior.

MTT Assay: Liposomes enhanced cellular uptake of talazoparib at early time points, and their temperature-sensitive release at 41°C further increased drug efficacy through rapid drug release. Consistent with previous studies, thermosensitive liposomes significantly improved drug activity at trigger temperatures. Cytotoxic effects were enhanced at both 39°C and 41°C.

Cellular Uptake of Rhamnosome and Cell Death Analysis: Rhamnolipid-containing liposomes exhibited higher cellular uptake than both the free drug and rhamnolipid-free liposomes, with this effect evident from 1 to 4 h. Moreover, these formulations enhanced the efficacy of talazoparib via the apoptotic pathway, while only minimal levels of necrosis were observed across all groups.

Conclusion: It was determined that the cytotoxic properties were enhanced with rhamnolipid addition. The anticancer effects of rhamnolipids have been previously demonstrated in many studies. In our study, similar results were obtained.

Acknowledgement: This study was supported by the TÜBİTAK (223S763)

POSTER PRESENTATIONS

(The abstracts are arranged in alphabetical order.)

LOW-VOLUME DISSOLUTION AS A DISCRIMINATORY EARLY-STAGE SCREENING TOOL FOR OCULAR DRUG DELIVERY SYSTEMS INTEGRATED WITH PHARMACOKINETIC MODELING: PROOF-OF-CONCEPT USING LEVOFLOXACIN NANOFIBER INSERT

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Introduction: Early-stage development of ocular formulations requires discriminatory in vitro tools to identify promising candidates before proceeding to costly and time-consuming biological and in vivo studies. Conventional dissolution tests commonly use 20–100 mL of medium, substantially exceeding physiological tear volume (7–30 μL). Such conditions may cause excessive dilution and mask formulation-dependent mechanisms related to viscosity, polymer swelling, gelation, and matrix properties.

Aim: To develop a practical 2 mL dissolution method with improved discriminatory capacity for early-stage screening of ocular formulations and integrate release data with pharmacokinetic modeling to support formulation selection.

Methods: Levofloxacin (LEVO)-loaded nanofibrous inserts were used as a proof-of-concept formulation. Drug release in the developed 2 mL system was compared with conventional 40 mL conditions using Weibull modeling and model-independent difference (f_1) and similarity (f_2) factors. Pharmacokinetic simulations compared once- and twice-daily inserts with eye drops administered every 2 h, incorporating release kinetics, ocular volume constraints, literature-based clearance assumptions, and pathogen-specific MIC/MBC thresholds.

Results: The 2 mL system showed slower, diffusion-controlled release (d = 0.915) compared with rapid release in 40 mL (d = 0.159), with clearly different profiles (f_1 = 27.74; f_2 = 21.37). Reduced volume revealed viscosity-related gelation effects masked under large-volume conditions. Pharmacokinetic modeling predicted prolonged therapeutic LEVO concentrations with twice-daily inserts compared with 12-times-daily eye-drop administration.

Conclusion: Low-volume dissolution provides a practical approach for discriminating formulation-dependent release behavior during early development. Its discriminatory potential may be particularly valuable when comparing formulations based on water-soluble and water-insoluble polymers with distinct release mechanisms. The method could enable early ranking and selection of candidates according to the desired release profile before proceeding with time-consuming and costly experiments. Integration with pharmacokinetic modeling may further support rational formulation and dosing decisions while reducing development time, cost, and experimental effort.

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ISOLATION AND PRELIMINARY CHARACTERIZATION OF EXTRACELLULAR VESICLES FROM 5 DIFFERENT ACUTE MYELOID LEUKEMIA CELL LINES FOR AML THERAPY

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Objective: The aim of this study is to identify and characterize exosomes derived from 5 different cell lines that can be used to develop a potential drug delivery system for the treatment of AML. Materials and Methods: The AML cell lines used in this study, arranged according to increasing maturation, were KG-1, Kasumi-1, HL-60, THP-1, and U937. Under optimized culture conditions, the cells were incubated with exosome-free medium for 48 hours. After incubation, the samples were centrifuged at 100,000 × g to perform isolation. To determine cell proliferation, cells were cultured under different medium conditions, and their growth kinetics were observed. Exosomes were isolated using the ultracentrifugation method from the AML cell line and the quantity of purified exosomes was determined with bicinchoninic acid (BCA) assay. The isolated exosomes characterized in terms of size, morphology, and surface properties by TEM, Western blot, flow cytometry, and NTA analyses.

Results: No significant difference in proliferation was observed between Exo-Free and Complete media for the Kasumi-1 cell line ($p = 0.1934$), whereas culture conditions had a significant impact on the proliferation of all other cell lines ($p < 0.001$). Among cells cultured and passaged in Complete medium, Kasumi-1 and KG-1 exhibited the slowest proliferation kinetics ($p = 0.8779$). Exosome production was also found to be lower in the less mature KG-1 and Kasumi-1 cell lines. Following a 2-hour ultracentrifugation at 100,000 × g, exosome aggregation was observed. Subsequent optimization of the protocol allowed exosome isolation to be achieved using a 90-minute centrifugation step. The particle sizes of the isolated exosomes were 137.6 ± 13.6, 143.6 ± 17.3, 206.3 ± 4.1, 240.5 ± 8.6, and 182.4 ± 4.0 nm, respectively. Isolated exosomes were expected to express at least one of the canonical markers CD9, CD63, or CD81. Western blot analyses of isolated exosome confirmed the presence of CD9, CD63, and CD81 in the corresponding cell lysates. Flow cytometry analysis revealed that CD9 exhibited the lowest mean fluorescence intensity (MFI), whereas CD63 and CD81 displayed higher MFI values relative to CD9. The Western blot results for CD9 and CD81 were consistent with the flow cytometry data, corroborating the marker expression profiles.

Conclusion: The results obtained provide new insights into method optimization for exosome isolation from 5 different AML cell lines.

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FORMULATION, CHARACTERIZATION AND IN VITRO EVALUATION OF MOXIFLOXACIN LOADED IN SITU GEL FOR OCULAR DRUG DELIVERY

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The eye is an important sensory organ that enables the visual perception of the external environment, which is vital for human life. In addition, eye infections are one of the most common health problems. In eye infections, eye drops are generally preferred. Solution-based formulations have disadvantages such as low bioavailability, ocular residence time, and application frequency. New pharmaceutical forms are being developed to eliminate the limitations of traditional drug forms and to enhance treatment efficacy.

In our study, aimed to improve an in situ gel system that increases ocular residence time and bioavailability while reducing application frequency. In situ gel systems are pharmaceutical dosage forms that change from solution form to gel form (sol-gel) with three different mechanisms. In the study, a moxifloxacin-loaded in situ gel exhibiting sol-gel transition depending on temperature was prepared and characterization tests were conducted. The formulations were prepared using different proportions of P188, P407, and methylcellulose.

The gelation temperature of the in situ gel formulation was obtained as 32.80±0.61°C. This temperature is consistent with ocular surface temperature, which is approximately 32–34 °C. With the gelation capacity tests, it was determined that the solution form changed to gel form in 4.85±0.58 seconds after application. pH range is important in eye formulations. In the test results, the pH value is 6.86±0.17 and these values remain in the human tear fluid. Viscosity tests were performed at refrigerator condition of 4°C and eye temperature/gelation temperature of 32°C. The viscosity value

of 4°C was found to be 24.00±4.00 cP and the viscosity value of 32°C was found to be 2873±11.55 cP. Drug loading efficiency was found to be 99.33±0.23%. Mechanical properties were evaluated at 32°C with a texturing device and hardness, adhesiveness, springiness, cohesiveness, and resilience were analyzed. Spreadability studies were performed at 4°C and 32°C in the texturing device. An increase in spreadability was observed with the rise in temperature. In addition, bioadhesion studies were performed with a texture device. Rheology study tests were performed. As a result, the formulation exhibited non-Newtonian pseudoplastic flow. An in vitro release study has been conducted. In this study, tear fluid was used to simulate the eye environment. The in situ gel formulation has been proven to demonstrate superior sustainable efficacy compared to the solution forms. It has been determined that the developed formulation prolongs drug release, increases bioavailability, demonstrates high bioadhesive and increases ocular residence time. Moreover, the formulation has high patient compliance with low frequency of application. The developed formulation exhibits new potential in the treatment of eye infections.

INFLUENCE OF POLYMERIC AND MESOPOROUS CARRIERS ON THE STABILITY OF AMORPHOUS RESVERATROL-LOADED SOLID DISPERSIONS OBTAINED BY HOT-MELT EXTRUSION

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Polymeric carrier choice and mesoporous carrier properties determine whether the drug remains in a stable amorphous state in solid dispersions during storage. In ternary amorphous solid dispersions, the mesoporous carrier provides nanoscale confinement while the selected polymer controls crystallization inhibition, supersaturation, and long-term amorphous stability *via* hydrogen bonding and pore-filling-dependent suppression of recrystallization (1–3).

The aim of this study was to evaluate the influence of polymer type, mesoporous carrier, and their combinations on the stability of amorphous resveratrol (RSV)-loaded solid dispersions obtained by hot-melt extrusion (HME).

Solid dispersions were prepared using individual polymers (PEG 6000, Eudragit® EPO, HPMC AS) and their mixtures with PEG 6000 at different ratios, combined with mesoporous silica carriers (Syloid® 244 FP or Neusilin® US2). RSV loading ranged up to 40% (w/w). Solid-state properties were evaluated by differential scanning calorimetry immediately after extrusion and after three months of storage under accelerated conditions.

All formulations showed reduced RSV melting enthalpy compared with crystalline RSV, indicating partial amorphization after processing. Storage resulted in variable changes in melting enthalpy across formulations, reflecting differences in physical stability. Polymer composition influenced storage-related behavior, with PEG-rich systems generally showing lower melting enthalpy, while differences between polymer combinations indicated formulation-dependent recrystallization tendencies. Differences between mesoporous carriers were less pronounced, with Syloid® generally showing lower melting enthalpy after storage than Neusilin®.

Overall, storage-related recrystallization behavior was influenced by both polymer composition and mesoporous carrier selection.

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SYNTHESIS OF CANNABINOIDS WITH ANTIMALARIAL EFFECT

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Cannabidiol (CBD) and cannabigerol (CBG) are non-psychotropic phytocannabinoids found in *Cannabis sativa*. These compounds interact with a wide range of receptors and biological targets throughout the human body, giving rise to numerous beneficial pharmacological effects that are currently under intensive investigation. Despite their growing popularity and therapeutic potential, the widespread application of CBD and CBG is significantly hindered by their poor water solubility and low bioavailability. To overcome these limitations and enhance their biological activity, our aim is to synthesize novel derivatives. Furthermore, since CBD has previously been reported to exhibit weak antimalarial activity, our study also aims to evaluate the antimalarial efficacy of these synthesized derivatives.

We have successfully synthesized CBD and CBG derivatives *via* Williamson ether synthesis using various nitrogen-containing alkylating agents. The introduction of the amino group enabled salt formation, which significantly increased the water solubility of the compounds. Biological evaluation revealed that these synthesized derivatives exert potent antimalarial activity.

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REACTION OF (E)-3-(4′-X-BENZYLIDENE)-4-THIOCHROMANONES WITH CELLULAR THIOLS. SHORT-RANGE ELECTRONIC ASSISTANCE AT THE TRANSITION STATE IN THE 4-SULFUR AND 4-OXYGEN ANALOGS OF (E)-2-(4′-X-BENZYLIDENE)-1-TETRALONE IN THIA-MICHAEL REACTIONS

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Introduction: Chalcones (1) are natural compounds that have several advantageous biological effects. Some of these effects have been reported to be associated with their thiol reactivity. Earlier, one thiochromone chalcone analog was reported to show inhibitory activity against the coronavirus main protease (SARS-CoV-2 Mpro). The latter possesses an active cysteine motif, which can be targeted by α,β-unsaturated ketones, leading to covalent modification of the enzyme. Besides the possible molecular mechanisms underlying their biological actions, reactivity toward glutathione is also a potential metabolic pathway of the compounds.

Aims: In our previous studies, we performed experiments to determine the thiol reactivity of some cyclic chalcone analogs (E)-2-(4′-X-benzylidene)-1-tetralones (2) and (E)-3-(4′-X-benzylidene)-2,3-dihydro-1-benzopyran-4-ones (3). In the present work, we aimed to perform similar experiments with their sulfur analogs, (E)-3-(4′-X-benzylidene)-4-thiochromanones (4), to seek a relationship between the thiol reactivity of the related compounds with the same aromatic substitution pattern but different ring structures. We performed the experiments at three selected pH values (3.2, 6.3, and 8.0) using reduced glutathione (GSH) and N-acetylcysteine (NAC).

Methods: Chalcone(2-4)-GSH/NAC (1:10 molar ratio) incubates were prepared (75% methanolic solution) using aqueous thiol solutions of three pH values (3.2, 6.3, and 8.0). The incubates were kept in a 37◦C water bath in the dark. Samples were withdrawn at 0, 15, 45, 75, 105, 135, 165, 195, 225, 255, 285, and 315 time points to monitor progress of the reactions. To analyze the samples, a suitable HPLC-UV method was developed. The

structure of the formed adducts was verified by HPLC-HESI-MS.

Results: The thiochromone (4) derivatives (X = H, CH3, OCH3) showed significantly higher thiol reactivity than the corresponding 6-membered carbocyclic chalcone (tetralone) analogs (2) [1]. Under pH 8.0 conditions, their NAC-reactivity followed the X=H>CH3>OCH3 order. A similar reactivity order was observed with both thiols at pH 6.3 and 3.2. In the reactions, four diastereomeric adducts were formed, which can only be partially separated under our HPLC-UV conditions. Comparison of the reactivities of the members of the three series with the same aromatic substituents showed a 3 > 4 >> 2 order under all three pH conditions. The reactivity of the 3 [2] and 4 series was found to be higher than that of the respective open-chain 1 derivatives under most of the investigated conditions.

Conclusions: The observed results can be explained by the different stability (degrees of delocalization) of the negatively charged intermediate in the addition process. It is affected both by the nature of the aromatic substituents and the structure of the cycloalkene ring. This latter can influence the stability of the intermediate by inductive, resonance, and conformational effects. This phenomenon is an example of intramolecular catalysis, known as transition-state electronic assistance.

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IN VITRO MODEL FOR THE PERMEATION ENHANCER EFFECT OF CYCLODEXTRINS

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Introduction: Cyclodextrins are cyclic oligosaccharides widely used as penetration enhancers in pharmaceutical and cosmetic formulations. Their unique structure, featuring a hydrophobic cavity and hydrophilic outer surface, allows them to form inclusion complexes with poorly soluble drugs. This complexation improves drug solubility, stability, and bioavailability. In terms of penetration enhancement, cyclodextrins facilitate drug transport across biological membranes by interacting with membrane lipids, temporarily altering membrane integrity and promoting permeation without causing significant irritation or toxicity. This is a very complex feature which is hard to capture with in vitro permeation models such as the parallel artificial membrane permeability assay (PAMPA).

Aims: The aim of this study was to see the effects of cyclodextrins on membrane permeability and integrity in a PAMPA-like system, where in situ UV-probes make concentration monitoring of the active pharmaceutical ingredient possible and membrane integrity measurements available in real time.

Methods: Small volume flux assay on μFlux. The formulations were tested using MicroFLUX™ apparatus. Concentration in both chambers was monitored in real-time using in situ fiber optic dip probes connected to the Rainbow instrument (Pion Inc.). A PVDF membrane impregnated with 25μL n-GIT lipid mixture (cholesterol- containing) was applied to form a lipophilic barrier between the donor and the acceptor chamber.

Dynamic Light Scattering (DLS) measurements Malvern Zetasizer Pro instrument (Malvern Instruments Ltd, United Kingdom) equipped with the manufacturer's standard 633 nm laser source. The samples were analyzed having the solutions filled inside a quartz cuvette of 1.00 9 1.00 cm dimensions. The particle sizes were obtained from the autocorrelation functions recorded and processed by Zetasizer Software.

Results: Preliminary findings using hydroxy propyl-β-cyclodextrin (HPβCD) and ranitidine as a guest molecule indicate that a minimum concentration of 50 mg/mL HPβCD is required to enhance drug flux in the donor chamber. The increased speed of transport, however, does not cause the total loss of membrane integrity. HPβCD monomers were detected in the acceptor side of the permeation chamber by DLS, indicating that larger size, hydrophilic molecules are also able to penetrate the membrane. This effect is likely due to HPβCD's interaction with membrane components, particularly its ability to disrupt cholesterol within the membrane structure. By altering the lipid organization, HPβCD increases membrane permeability, allowing greater drug passage.

Conclusion: These results highlight the importance of sufficient cyclodextrin concentration to achieve a measurable penetration-enhancing effect. Lower concentrations may be insufficient to significantly modify membrane properties or improve drug transport across the barrier. Based on the results, it is important to emphasize that the

effects of cyclodextrins can only be accurately measured when real-time concentration monitoring is implemented on both the donor and acceptor compartments of the permeation system.

DEVELOPMENT AND CHARACTERIZATION OF 3D-PRINTED PREDNISOLONE ACETATE TABLETS: INFLUENCE OF FORMULATION AND PRINTING PARAMETERS ON DRUG RELEASE

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Three-dimensional (3D) printing technology offers significant potential for the individualization of therapy and the optimization of formulations containing poorly soluble active pharmaceutical ingredients such as prednisolone acetate. The incorporation of different excipients, as well as printing parameters including infill density and pattern, can influence the drug release rate from the resulting dosage forms. The aim of this study was to develop and characterize 3D-printed tablets containing prednisolone acetate and to investigate the influence of formulation composition and printing parameters (infill density and pattern) on the drug release profile. Filaments containing prednisolone acetate incorporated into a polyvinyl alcohol matrix, with the addition of sorbitol and sodium alginate in selected formulations, were prepared by hot-melt extrusion, characterized, and subsequently used for the fabrication of 3D-printed tablets using fused deposition modeling. The tablets were evaluated in terms of mass variation, dimensions, mechanical strength, and dissolution rate. Extrusion of a mixture of polyvinyl alcohol and prednisolone acetate alone resulted in defective filaments, necessitating the addition of sorbitol. Filaments of formulations F2 (prednisolone acetate, sorbitol, and polyvinyl alcohol) and F3 (prednisolone acetate, sorbitol, polyvinyl alcohol, and sodium alginate) exhibited uniform structure and homogeneous drug distribution. The 3D-printed tablets met pharmacopeial requirements for mass variation and demonstrated good dimensional accuracy, reproducibility, and mechanical strength. Dissolution studies indicated that lower infill density accelerated drug release, while the presence of sodium alginate slowed release at higher infill densities and with a gyroid infill pattern. Overall, infill density was identified as the dominant factor affecting release kinetics. Sodium alginate did not significantly influence the dissolution profile in tablets with a linear infill pattern, regardless of infill density. Among the tested formulations, A100G (gyroid structure with 100% infill density), containing prednisolone acetate, polyvinyl alcohol, sorbitol, and sodium alginate, was identified as the most suitable for achieving sustained drug release.

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Keywords: 3D printing, printlets, drug release rate, FDM, HME, sodium alginate.

IMPROVING CLINICAL TRIAL FEASIBILITY

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Background: Clinical trial feasibility is a critical determinant of study success, influencing recruitment performance, protocol compliance, study timelines, operational efficiency, and overall research costs. Inadequate feasibility assessments frequently contribute to protocol amendments, delayed site activation, recruitment difficulties, and increased financial burden. Despite the operational importance of feasibility evaluations, Principal Investigators (PIs) are often involved only after protocol finalization, limiting opportunities to identify site-level challenges and patient-related barriers during protocol development.

Objectives: This research aims to investigate whether early involvement of Principal Investigators during protocol planning and feasibility assessment can improve clinical trial efficiency and reduce operational risks. The study specifically evaluates the impact of early PI engagement on protocol feasibility quality, amendment frequency, recruitment performance, startup timelines, and patient retention.

Methods: A mixed-method research design is applied, combining quantitative and qualitative approaches. The quantitative component includes retrospective analysis of clinical trial data, focusing on protocol amendments, recruitment timelines, screen failure rates, and site activation duration. The qualitative component includes questionnaires and semi-structured interviews conducted with Principal Investigators, Clinical Research Associates, Study Coordinators, and Clinical Project Managers involved in clinical trial operations. Data collection focuses on identifying operational challenges, feasibility assessment limitations, and the perceived value of early investigator input during study planning.

Expected Results: The study is expected to demonstrate that early PI involvement contributes to improved protocol feasibility, earlier identification of operational barriers, reduced amendment frequency, and enhanced recruitment planning. Additionally, investigator-inclusive feasibility processes may support more realistic protocol implementation and improve communication between sponsors and investigational sites.

Conclusion: Early Principal Investigator involvement may represent an effective and practical strategy for improving clinical trial feasibility and operational performance. Integrating investigator expertise during protocol development could contribute to more patient-centered, feasible, and efficient clinical studies while reducing avoidable delays and operational burden.

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VARIABILITY IN WITHANOLIDE CONTENT OF COMMERCIAL ASHWAGANDHA SUPPLEMENTS: A HPLC-ESI-MS/MS STUDY

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Ashwagandha (Withania somnifera), also known as winter cherry, is a key herb in Ayurvedic medicine and has gained increasing popularity in the Western world as a dietary supplement. It is known for its adaptogenic properties, it supports sleep quality, enhances physical performance, and alleviates stress-related symptoms, making it particularly appealing to athletes, individuals with high-stress lifestyles, and those suffering from sleep disorders. The plant's therapeutic potential is primarily attributed to steroidal lactone compounds known as withanolides.

In this study, analysis of commercial ashwagandha products was conducted using a validated HPLC-ESI-MS/MS method. From a wide range of available supplements, seven capsules from four different manufacturers and three powdered root products from three additional suppliers and an extract were selected to provide an overview of labeled active compound content. As a reference, a powdered root sample from Galke GmbH (Gittelde, Germany) – certified under BIO, Kosher, ISO 9001, ISO 14001, AEO, and GMP standards – was chosen as a reliable benchmark.

Withaferin A, one of the most abundant withanolides, was employed as the analytical standard for quantification. Due to its structural similarity to other withanolides, it facilitated the detection of related compounds sharing similar MRM fragmentation patterns. The HPLC-ESI-MS/MS method was validated according to the EMA guidelines, evaluating selectivity, accuracy, precision, recovery, carry-over, matrix effects, and stability. Our findings were corroborated by high-resolution UHPLC-ESI-Orbitrap-MS/MS, ensuring structural verification and methodological robustness. Results revealed that chemical profiles of powdered products were consistent with the reference material. In contrast, capsule formulations displayed substantial variability in bioactive compound content and profiles, largely attributable to differing extraction methods. Notable differences persisted even between batches from the same manufacturer. These observations underscore the lack of stringent regulation in the dietary supplement market, which can lead to inconsistent product quality and potential risks to consumers expecting reliable effects. This emphasizes the urgent need for standardized quality control frameworks to safeguard the safety and efficacy of ashwagandha supplements marketed for stress management and well-being.

ELECTROSPUN PVP-BASED LERCANIDIPINE NANOFIBER FORMULATION: DEVELOPMENT AND SOLID-STATE CHARACTERIZATION

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Introduction: Lercanidipine hydrochloride (LER) is a third-generation dihydropyridine calcium channel blocker used in the treatment of hypertension. Its poor aqueous solubility and extensive first-pass metabolism result in low and variable oral bioavailability (Chonkar et al., 2016). Electrospinning offers a promising approach to overcome solubility-related limitations by incorporating active pharmaceutical ingredients into high-surface-area polymeric fibrous matrices and facilitating their transition from crystalline to amorphous or molecularly dispersed states. Polyvinylpyrrolidone K90 (PVP K90) is widely used as a carrier in nanofiber formulations due to its hydrophilic nature and favorable electrospinnability (Muratoglu et al., 2024). This study aimed to develop an orodispersible PVP formulation loaded with LER via electrospinning and evaluate its morphological and solid-state characteristics.

Materials and Methods: LER (200 mg) was dissolved in 2 mL of ethanol by sonication, followed by the addition of 3 mL of a 16.66% (w/v) PVP solution. After further sonication to obtain a homogeneous solution, electrospinning was performed using a circular collector at an applied voltage of 12.5 kV, a flow rate of 40 μL/min, and a tip-to-collector distance of 13 cm for 1 h. The resulting formulation was characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), and X-ray diffraction (XRD), and compared with the starting materials.

Results: SEM revealed a heterogeneous matrix composed predominantly of flattened, ribbon-like fibrous structures with micron-scale features and smaller surface deposits. XRD analysis showed crystalline diffraction features for LER, whereas PVP exhibited a broad diffraction pattern consistent with its amorphous nature. In the electrospun formulation (NFBR), LER-related crystalline features were substantially reduced, and the diffraction pattern became predominantly diffuse, indicating a marked decrease in drug crystallinity. Consistently, the characteristic endothermic melting peak of crystalline LER observed by DSC was significantly reduced or absent after the electrospinning process, supporting its conversion to an amorphous or highly disordered state within the polymeric matrix. FTIR spectra retained the principal absorption bands of the individual components while exhibiting alterations in drug-related absorption bands, suggesting changes in the molecular environment of LER and potential interactions with PVP.

Conclusion: The developed electrospun system enabled the incorporation of LER into a PVP matrix, resulting in reduced drug crystallinity and increased molecular-level dispersion. Although the formulation exhibited a heterogeneous, ribbon-like morphology rather than uniform nanofibers, the findings demonstrate the potential of electrospinning to modify the solid-state properties of LER. Further optimization and dissolution studies are required to evaluate its potential biopharmaceutical benefits.

Keywords: electrospinning; Lercanidipine hydrochloride; nanofiber; polyvinylpyrrolidone

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CHALLENGES IN THE ORAL ADMINISTRATION OF GASTRO-RESISTANT FORMULATIONS: THE ROLE OF VEHICLES AND BOTTLED WATERS

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Background/Objectives: Gastro-resistant multiparticulate systems are designed to protect drugs in acidic environments and to ensure intestinal release. In practice, the method of administration may need to be modified: pellet-containing capsules opened or tablets halved for patients with swallowing difficulties, yet the type of liquid used for administration is often not specified. This study investigated the stability of gastro-resistant coated pellets after exposure to various aqueous media prior to ingestion.

Methods: To evaluate administration instructions, 103 Summaries of Product Characteristics of gastro-resistant products were reviewed. Pellets were produced using a bottom-spray fluidized bed process and coated with Eudragit L. The physicochemical properties of selected administration media were characterized based on pH and conductivity. Dissolution testing in pH 1.2 medium was performed after pre-soaking the pellets for 5, 15, and 30 min in beverages with various pH and conductivity. Drug release was measured by UV-VIS method. In addition, selected marketed gastro-resistant products were examined following exposure to different administration media.

Results: The SmPC review revealed considerable variability in administration instructions. In many cases, the vehicle was either not specified or was described only as a liquid, while clearly defined recommendations for suitable administration media were uncommon. The tested beverages showed substantial differences in pH and conductivity. Alkalizing medicinal and natural mineral waters markedly impaired the gastro-resistant performance of the pellets, with the effect becoming more pronounced with increasing pre-soaking time. In contrast, tap water had a considerably lower impact, while filtered water consistently resulted in the lowest drug release. The dissolution results demonstrated that both the administration medium and the duration of pre-soaking influenced the subsequent drug release from the gastro-resistant pellets. Similar differences were observed during the examination of marketed gastro-resistant products, with pronounced coating disruption following exposure to selected mineral waters.

Conclusions: The results indicate that contact with non-specified aqueous media before swallowing may compromise the protective function of gastro-resistant films. The composition of the administration liquid, together with the duration of exposure, may substantially influence coating integrity and consequently the release characteristics of gastro-resistant multiparticulate systems. More precise and explicit recommendations regarding suitable administration media for manipulated gastro-resistant dosage forms may reduce the risk of unintended premature drug release and improve therapeutic consistency and patient safety.

PHYTOCHEMICAL PROFILE, HEMOSTATIC AND WOUND HEALING ACTIVITIES OF EXTRACTS FROM DIFFERENT PARTS OF COMMON COMFREY (*SYMPHYTUM OFFICINALE* L.)

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BACKROUND: Common comfrey (*Symphytum officinale* L.) is widely used in different European countries' traditional medicine for the treatment of wounds, fractures, and soft tissue injuries. The most commonly used part of the plant is the root, which contains allantoin, a wound-healing promoting agent. The allantoin content is significantly lower in the leaves, however, leaf extracts have also shown promising wound healing activity. This suggest the presence of wound-healing compounds in the aerial parts as well. However, according to current knowledge, the phytochemical profile and pharmacological activity of *S. officinale* flowers and a comprehensive organ-specific phytochemical comparison of different plant parts remain unexplored.

AIM The aim of the study was to compare the phytochemical composition, in vivo hemostatic and wound healing activity of extracts obtained from different organs of *S. officinale* to identify the most pharmacologically active parts of the plant.

MATERIALS AND METHODS: Extracts from the roots, leaves, and flowers of *S. officinale* were prepared using solvents of different polarity, with a plant material-solvent ratio of 1:10. Phytochemical composition of dry extracts was analyzed by spectrophotometric assays and UPLC–MS/MS. Pharmacological activities were evaluated in vivo on Wistar rats. Hemostatic activity was assessed by measuring time to complete bleeding cessation, compared with untreated animals and those treated with *Persicaria hydropiper* extract. Wound healing activity was evaluated against untreated animals and "Rotokan" (mixture of tinctures derived from the flowers of *Matricaria chamomilla* and *Ca-*

lendula officinalis, and from the herb *Achillea millefolium*) on days 1, 4, 7, 10, 12, and 14, while cytological samples were collected on days 1, 3, and 7 of the wound healing process.

RESULTS: Distinct organ-specific differences in phytochemical composition were observed, with leaf and flower extracts richer in phenolic compounds and amino acids, while root extracts contained higher levels of pyrrolizidine alkaloids. In total, 12 phenolic compounds, 14 amino acids, and 8 pyrrolizidine alkaloids were identified. Extracts from leaves and flowers presented the highest diversity of phenolic compounds. Rosmarinic acid, caffeic acid, and isoquercitrin were identified as dominant constituents. Amino acid profiling revealed that extracts from flowers had the highest level of proline, aspartic acid, and glutamic acid, which are known to be involved in tissue regeneration. The solvent system used in extraction significantly influenced the phytochemical composition. The strongest biological activity was shown by the leaf extract prepared with 40% ethanol and the flower extract prepared with 70% ethanol. The flower extract accelerated wound healing, achieving complete closure by day 10, while the leaf extract exhibited the most pronounced hemostatic effect. Cytological analysis indicated that local application of plant extracts reduced inflammation and enhanced fibroblast activity. The findings support the traditional use of *S. officinale* in wound treatment and highlight the importance of organ-specific phytochemical composition. Aerial parts showed strong wound-healing and hemostatic effects, suggesting relevance alongside the traditionally used root and indicating the activity are likely attributed to the synergistic action of polyphenols and amino acids.

FUNDING: Estonian Research Council (ERC) grant (PRG1903)

Keywords: common comfrey; phenolic compounds; amino acids; pyrrolizidine alkaloids; hemostatic activity; woundhealing activity

A NOVEL IBUPROFEN-DERIVED H_2S DONOR (EV-34) WITH OPTIMIZED RELEASE KINETICS ATTENUATES DOXORUBICIN-INDUCED CARDIOTOXICITY

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Doxorubicin (DOX) is a widely used chemotherapeutic agent effective against numerous solid and hematological malignancies; however, its clinical utility is significantly limited by cumulative, dose-dependent cardiotoxicity. Despite extensive research, the precise molecular mechanisms underlying DOX-induced cardiac injury remain incompletely understood, and effective cardioprotective interventions are still lacking. Emerging evidence highlights a critical role for disrupted endogenous hydrogen sulfide (H_2S) biosynthesis in mediating DOX-induced cardiomyocyte damage.

In this study, we investigated EV-34, a newly synthesized ibuprofen-based H_2S-releasing compound specifically designed according to the methodology described by Gyöngyösi et al. We demonstrate that EV-34 significantly attenuates DOX-induced cardiotoxicity by reducing oxidative stress, mitochondrial dysfunction, and apoptotic cell death. Mechanistically, EV-34 elevates intracellular H_2S levels under both basal and DOX-treated conditions via a dual mode of action, combining direct H_2S donation with stimulation of endogenous H_2S production pathways.

Furthermore, EV-34 suppresses reactive oxygen species (ROS) generation, decreases mitochondrial superoxide accumulation, and enhances mitochondrial antioxidant defenses, as evidenced by increased superoxide dismutase levels. At the signaling level, EV-34 exerts its cardioprotective effects through activation of the PI3K/AKT/FoxO3a and AMPK pathways, alongside inhibition of apoptosis via suppression of caspase-3 activation.

Collectively, these findings identify EV-34 as a promising therapeutic candidate for the prevention and management of DOX-induced cardiotoxicity. Notably, its effects were benchmarked against the well-characterized slow-releasing H_2S donor GYY4137.

FROM VISUAL INSPECTION TO QUANTITATIVE CHARACTERISATION: EXPLORING IMAGE ANALYSIS APPLICATIONS IN PHARMACEUTICAL TECHNOLOGY

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Visual inspection is one of the oldest methods described in pharmacopoeias for the identification and characterisation of active pharmaceutical ingredients, excipients and pharmaceutical dosage forms. Advances in digital imaging technologies have enabled visual assessment to be complemented by objective and quantitative image analysis, providing reproducible information on changes that may be difficult to evaluate by conventional inspection.

The aim of this study is to present novel applications of image analysis in pharmaceutical technology and to demonstrate how established imaging techniques can be used in new ways for process monitoring and the characterisation of pharmaceutical systems.

Digital image analysis was used to evaluate changes in the systems during processing, storage and testing. Images were acquired using a digital microscope and analysed with ImageJ software. Image processing and analysis procedures were applied to obtain quantitative parameters and monitor changes over time or under different experimental conditions.

The investigated applications demonstrated that image analysis can provide useful quantitative information during pharmaceutical processing, storage and product characterisation. Changes in pellet coating, tablet colour, lyophilised tablet wetting and pellet behaviour in different media could be objectively monitored and evaluated using image-based parameters. The results demonstrate that image analysis can provide additional information alongside conventional analytical methods and can be adapted to different pharmaceutical applications.

The presented examples demonstrate how established image analysis techniques can be applied in novel ways in pharmaceutical technology. The approach provides a simple and reproducible means of monitoring visual and physical changes and can support process control, stability assessment and product characterisation. These applications further broaden the practical use of image analysis in pharmaceutical technology.

INVESTIGATION OF *CENTAURIUM ERYTHRAEA* EXTRACT-CONTAINING OINTMENT FORMULATIONS FOR ANTI-INFLAMMATORY AND ANTIOXIDANT EFFECTS

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Background: *Centaurium erythraea* Rafn. (*C. erythraea*) is a medicinal plant traditionally used in European folk medicine for the treatment of wounds, skin inflammations, and other dermatological conditions, in addition to its well-documented systemic antioxidant and anti-inflammatory effects. However, its topical applications remain insufficiently investigated, particularly using plant material collected from Romania. The purpose of this study was to prepare different ointment formulations containing *C. erythraea* Rafn. extract obtained from the aerial parts of the plant, using various excipients, and to evaluate their *in vitro* and *in vivo* efficacy.

Methods: The phytochemical profile of *C. erythraea* extract was characterized using liquid chromatography–tandem mass spectrometry (LC–MS/MS). The lyophilized extract was pre-dissolved in different solubilizing agents—Transcutol® P (diethylene glycol monoethyl ether), Capryol® 90 (propylene glycol monocaprylate), or a combination of both—and then incorporated into five ointment formulations. Texture analysis and an *in vitro* membrane diffusion study were performed. The antioxidant capacity of the formulations was assessed by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging, ferric reducing anti-

oxidant power (FRAP), and total phenolic content (TPC) assays. Anti-inflammatory activity was evaluated i*n vitro* using tumor necrosis factor-alpha (TNF-α)-induced interleukin-1 beta (IL-1β) production in human keratinocyte (HaCaT) cells, and *in vivo* using a carrageenan-induced rat paw edema model. Results: LC–MS/MS identified 18 polyphenolic compounds, with hyperoside (3.78 ± 0.05 μg/mL), protocat echuic acid (1.13 ± 0.06 μg/mL), chlorogenic acid (1.07 ± 0.06 μg/mL), and quercetin (0.53 ± 0.03 μg/mL) as the principal constituents. The formulation containing both Transcutol® P and Capryol® 90 exhibited the most pronounced antioxidant activity (65% DPPH inhibition; 69.71 ± 0.83 mg gallic acid equivalent/mL) and significantly reduced IL-1β levels by 45.7% compared to the inflamed control. *In vivo*, this formulation showed comparable anti-edematous effects to a methylprednisolone ointment. Furthermore, it demonstrated the highest skin permeation efficiency, with a quercetin diffusion coefficient of 35.12×10^{-5} cm^2/min.

Conclusions: These findings highlight the therapeutic potential of *C. erythraea* extract from aerial parts in topical formulations and underscore the enhancing role of Transcutol® P and Capryol® 90 in improving both the pharmacodynamic and pharmacokinetic properties of bioactive compounds.

CYCLODEXTRIN COMPLEXATION STUDY OF DIARYLHEPTANOIDS ISOLATED FROM ALPINIA OFFICINARUM

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Lesser galangal (Alpinia officinarum Hance, Zingiberaceae) is a key plant in Southeast Asian traditional medicine and possesses a complex profile of bioactive compounds. Among its promising constituents, diarylheptanoids exhibit numerous beneficial effects; however, their instability and poor water solubility limit their bioavailability. Cyclodextrins (CDs) are suitable for improving these properties, as they form non-covalent inclusion complexes that enhance the physicochemical characteristics of the encapsulated molecules.

The main goal of our work was to improve the bioavailability of the isolated compounds from the lesser galangal rhizome through CD complexation. To achieve this, we aimed to develop an affinity capillary electrophoresis (ACE) method that enables rapid and comprehensive investigation of complex formation between eight isolated compounds and various CD derivatives. ACE is a widely applied technique for the cost-effective and environmentally friendly investigation of interactions between analytes and CDs. During the measurements, changes in the effective mobility of analytes were monitored as a function of CD concentration, allowing the determination of the complex stability constants. Our further aim was to validate and use an UHPLC-DAD method to monitor the CD-induced improvements in the stability and solubility of the studied diarylheptanoids.

In our comprehensive ACE studies, we examined the complex-forming properties of several negatively and positively charged CD derivatives using eight structurally different Alpinia diarylheptanoids. We found that the stability of the formed inclusion complexes is influenced by the cavity size of the CD, as well as its charge and the type of substituents. Based on the ACE results, the most promising CDs were selected to investigate their effects on the stability and kinetic solubility of diarylheptanoids.

The selected CDs may be suitable in the future for enhancing the solubility and stability of phenolics with unfavorable bioavailability, thereby facilitating their pharmaceutical formulation.

PREPARATION AND CHARACTERISATION OF LEVOTHYROXINE-CONTAINING SUPPOSITORIES: THE ROLE OF PARTICLE SIZE AND DISPERSION SYSTEM ON DRUG RELEASE

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Background: Early diagnosis and appropriate treatment of congenital hypothyroidism are essential for normal neurological development. [1] Levothyroxine (LT4) is the first-line therapy for hypothyroidism; however, currently available dosage forms—primarily tablets, capsules, and liquid formulations (per os, intramuscular, intravenous, subcutaneous) - may be limited in neo-

nates due to difficulties in administration, absorption issues, and lack of patient compliance. [2][3] Therefore, alternative routes of administration, such as rectal delivery, have been proposed. In this context, levothyroxine administered as a suppository may represent a promising option, particularly in pediatric care [3].

Aims: The aim of this study was to prepare levothyroxine-containing suppositories with the active ingredient of different particle sizes and type of distribution (suspension and emulsion), and to investigate how particle size, type of drug distribution, and manufacturing technology influence drug release.

Methods: Preparation of suppositories: Suppositories were prepared using conventional moulding and 3D printing techniques. Suppocire NAI 25 A pellets (Gattefossé) were used as the base. The sodium salt of LT4 was prepared using sodium hydroxide. In emulsion-type suppositories, inverse emulsions were stabilised with nonionic surfactants, and surfactant concentrations were calculated based on droplet size and space filling. For suspension-type suppositories, LT4 nanocrystals of different sizes were obtained by reacidification of alkaline LT4 solution under varying conditions.

Characterisation: Particle size was determined by dynamic light scattering (DLS).

The drug release studies were performed using spectrophotometric and amperometric methods.

Results: Drug release rates were compared to those of suppositories prepared from powdered commercial tablets. Photometric methods were not suitable for monitoring the release due to the several-minute sample preparation time. Using electrochemical methods, the slowest drug release was observed in the powder-based suppositories (300 s), while the fastest release was measured for emulsion-based suppositories (100 s).

Conclusions: The study is expected to provide insight into how particle size, type of the dispersion system, and manufacturing method influence the release and release kinetics of levothyroxine from suppositories. The results may contribute to the development of an alternative dosage form with improved applicability in neonates and infants.

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EVALUATION OF ANTIBIOTIC USE IN PATIENTS ADMITTED TO A HUNGARIAN INTENSIVE CARE UNIT WITH PNEUMONIA AND SEPSIS: RETROSPECTIVE OBSERVATIONAL BEFORE–AFTER STUDY

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Background: Early and adequate empiric antibiotic therapy is essential in the treatment of pneumonia and sepsis and may influence the clinical outcome.
Aims and Objectives: This retrospective before–after study aimed to appraise the impact of a local Antibiotic Stewardship Program (ASP—written guidelines and antibiotic restriction) on antibiotic (AB) use and clinical outcomes in patients requiring intensive care due to pneumonia and sepsis.
Methods: This study was conducted as a single-center, retrospective observational study in the intensive care unit (ICU) of a pulmonology department of a tertiary care center. Data were collected for the pre-intervention period between January 2018 and May 2022 and for the ASP period between June 2022 and March 2024. In addition to descriptive statistics and univariable methods, interrupted time series (ITS) analysis was used to assess AB use and length of stay in the ICU before and after ASP implementation, using a segmented linear regression with a fixed breakpoint and continuous (hinge) specification.

Results and discussion: The patients admitted

to the ICU with pneumonia and sepsis were mainly men (58/101, 57.4% and 84/128, 65.6%), the need for intensive care increased with age, and most of the patients belonged to 65+ age group in both study phases (69/101, 68.3% and 75/128, 58.6%). The majority of the patients had four or more comorbidities (58/101, 57.4% and 52/128, 40.6%). In-hospital mortality was relatively high (42.6% and 41.4%), with most of the patients losing their lives in the ICU (33/43, 76.7% and 37/53, 69.8%). Significant increase in guideline-adherent agent selection (34.5%) and use of combination therapy (35.0%) was observed, while the use of fluoroquinolones decreased significantly (−31.1%). In the after period, a significant decrease in the number of patients using restricted ABs (−53.3%) was observed. In one-third of these cases (10/34, 29.4% and 16/40, 40%), two to four multidrug-resistant pathogens (MDRs) were detected simultaneously, resulting in a significant increase in direct costs (10.5%) in the ICU. The inappropriate use of AB therapy was relatively low in the presence of MDRs in both phases (2/34, 5.9% and 6/40, 15%). In the ASP period, guideline adherence was associated with slightly better clinical outcomes (30-day mortality: −0.8%; length of stay: −22.6%) in pneumonia and sepsis. The ITS analyses after the ASP implementation showed a weak downward trend and before it a slight increasing trend. Conclusions: ASP implementation in the ICU resulted a significant improvement in the appropriate use of ABs, and guideline adherence led to slightly better clinical outcomes. Our results suggest that ASP may offer improved antimicrobial resistance with a sustained long-term effect.

STEADY-STATE CONCENTRATIONS OF CLARITHROMYCIN UNDER DIFFERENT ROUTES OF ADMINISTRATION IN PNEUMONIA: RISK-FACTORS AND CLINICAL OUTCOMES

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Background: Appropriate antibiotic dosage is crucial for improving outcomes in critically ill patients facing pneumonia.

Aims: Our research aimed to evaluate the development of the steady-state concentration (Css) of clarithromycin (CLAR) in this specific patient population with different routes of administration, to identify the influencing factors, and to examine the relationship between clinical outcomes and Css.

Methods: This study was conducted as a single-center prospective observational study in the ICU of a pulmonology department between 02 February 2025 and 05 December 2025. The study target group included all adult patients (n=72) treated primarily with empirical CLAR (500 mg two times a day, n=70 cases; corrected to kidney function, n=2 cases) due to pneumonia. Blood sample collection was performed on day 3 of the CLAR administration, when 5 samples were taken as follows: at steady-state before drug administration and 1, 2, and 3 hours after intravenous (IV), oral (PO), and nasogastric (NG) drug administration, while 1one sample for albumin level. Serum concentrations of CLAR was determined by LC-MS/MS using a CLAR European Pharmacopeia Reference Standard by Merck. The study received ethics approval (DE RKEB/IKEB: 7094-2025).

Results and discussion: CLAR serum levels followed the expected pharmacokinetics for all three routes of administration. The CLAR Css was 3-fold higher for PO (n=30) than for IV (n=27) administration and 2.7-fold higher for NG (n=15) administration (6.13 vs 2.05 μg/ml and 6.13 vs 2.26 μg/ml, $p<0.05$). Severe reduction of CrCl (<59ml/min) increased serum levels for all administration routes. CLAR serum levels increased proportionally with increasing albumin serum levels (as the faster clearance of the free fraction resulted in lower serum levels, especially for IV) and with the increasing CCI (Charles Comorbidity Index). No significant difference in length of stay (LOS) and in survival was found between IV and PO administration (81 and 83%), however, the probability of survival was significantly lower (40%) in the case of NG administration.

Conclusions: PO administration presented the highest CLAR Css levels. CrCl, albumin levels, and CCI were found to be influencing factors of CLAR Css. PO and IV administration resulted in similar clinical outcomes; however, the lower survival rate associated with higher Css values in case of NG administration requires further investigation.

LIQUID CRYSTALLINE NANOPARTICLES: EVALUATION OF ENCAPSULATION EFFICIENCY OF DIFFERENT DRUGS

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Liquid crystalline nanoparticles (LCNPs) combine the structural features of lyotropic liquid crystals with the advantages of nanoparticles, representing a unique nanodelivery system. Their dispersions, called cubosomes or hexosomes, are formed by the self-assembly of specific amphiphilic lipids in an aqueous environment. They enable encapsulation of hydrophilic, hydrophobic, and amphiphilic drugs, providing protection from degradation and sustained release, while being biocompatible and biodegradable with cost-efficient production (1–2).

The aim of this study was to evaluate encapsulation efficiency (EE) of drugs with different physicochemical properties, i.e. betamethasone dipropionate, paracetamol, metformin, and peptide drug thymosin alpha 1, in set of LCNPs differing in preparation approach.

LCNPs were composed of glyceryl monooleate (lipid and mesogen), poloxamer 407 (steric stabilizer) and ethanol (hydrotropic agent) as main components and prepared using either high-energy »top-down« or low-energy »bottom-up« methods. The resulting loaded and unloaded LCNPs were characterized by their mean particle size and polydispersity index using dynamic light scattering, while EE was determined by ultrafiltration and subsequent high-performance liquid chromatography with separation and analytical conditions tailored to each drug.

Through experiments, stable dispersions of LCNPs were obtained, with smaller nanoparticles obtained using a top-down method. Both methods were proved suitable for the incorporation of small therapeutic molecules as well as larger peptide drug, with EE influenced by the drug's size, lipophilic/hydrophilic character and ionization state, highlighting the need for a drug-tailored LCNPs formulation approach.

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PREDICTING POWDER DOSING BEHAVIOR FROM BULK POWDER IMAGES USING NEURAL-NETWORK EMBEDDINGS

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Twin-screw powder feeders often show a loss of dosing stability over time. One possible cause is powder adhesion to the screw surface, which may reduce the effective displacement volume of the screw and consequently decrease powder throughput. Previous studies have investigated the dosing behavior of different powders and attempted to correlate powder properties with feeding performance (1,2). However, powder dosing is generally not governed by a single material property, but rather by a complex interaction of multiple physical phenomena, including cohesion, adhesion, wall friction, bulk density, compressibility, and electrostatic effects(3). Because no single measured powder property adequately explained the observed flow behavior, we explored an alternative approach based on image analysis. In this study, bulk powder images were analyzed using neural network image embeddings. These embeddings were treated as powder descriptors and correlated with the flow behavior of the corresponding mixtures during dosing.

Eighteen mixtures containing different fillers and glidants were prepared. The fillers included Lactose Mesh 200, Lactose SD14, Mannitol M100, Avicel PH200, Avicel PH101, PVP K-25, and Pharmacoat 606. The glidants were magnesium stearate, Aerosil 200, talc, and Tricafos 200-7. Powder batches of 300 g were dosed using a twin-screw feeder (MT-S HD, Brabender), and the mass flow rate was monitored gravimetrically using a balance (XP4002S, Mettler Toledo). Flow behavior was evaluated at three screw speeds: 15, 30, and 45 rpm. In general, higher screw speeds resulted in a lower relative standard deviation of the flow rate. Among the tested glidants, magnesium stearate produced the highest powder throughput under comparable conditions.

Powder images were acquired by optical scanning of the bulk material at 1200 dpi with 24-bit color depth. The resulting images, with a resolution of 10,182 × 7,011 pixels, were divided into 448 × 448 pixel tiles and embedded using the DINOv2 neural network model. The image embeddings were divided into stratified training and test sets in an 80:20 ratio. Logistic regression, support vector machines, and random forest classifiers were then used to classify the mixtures based on the embeddings. The highest classification accuracy reached 85%, which was notable because some mixtures differed only in glidant concentration.

Finally, the image embeddings were correlated with selected powder flow characteristics. The results suggest that image derived descriptors may provide a promising approach for evaluating bulk powder mixtures and predicting their dosing behavior from visual appearance.

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DESIGN AND FABRICATION OF 3D-PRINTED TRANSDERMAL PATCHES FOR CO-DELIVERY OF HORMONES AND NK3 INHIBITORS

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The cause of menopause is the disruption of hormonal homeostasis, which is accompanied by a decrease in oestrogen levels. These changes may lead to symptoms and diseases, including cardiovascular alterations, osteoporosis, hot flushes, vaginal dryness, and decreased libido. Although various forms of hormone therapy are available, none provide a comprehensive therapeutic solution, therefore, the demand for innovative medicinal products is continuously increasing. The aim of the present research is to develop an oestrogen and NK-3 receptor inhibitor releasing transdermal drug delivery system that ensures appropriate bioavailability of the active pharmaceutical ingredient through a cyclodextrin–polymer complex.

The formulation development was carried out based on the Quality by Design (QbD) approach. Critical quality attributes (pH, tensile strength, adhesion and moisture content) were optimized using factorial experimental design. The pH range of the prepared patches corresponds to the physiological values of the skin environment, its low moisture content ensures stability, and its high tensile strength and adhesion allows application using on the skin. The scaffold was produced using 3D printing, taking into account the need for customization based on the patient's individual medication regimen.

In conclusion, the developed oestrogen and NK-3 receptor inhibitor containing film and scaffold may represent an innovative therapeutic alternative that effectively alleviates the most common symptoms of menopause, thereby contributing to an improvement in women's quality of life.

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LINALOOL AND GERANIOL DEFEND NEURONS FROM OXIDATIVE STRESS, INFLAMMATION, AND IRON ACCUMULATION IN IN VITRO PARKINSON'S MODELS

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Parkinson's disease is one of the most prevalent neurological disorders affecting millions of people worldwide (1). There is a growing demand for novel and natural substances as complementary therapies. Essential oils and their various compounds are highly investigated natural plant-based products as potential treatment options for common human diseases, such as microbial infections, chronic diseases, and neurodegenerative disorders (2). The present study focuses on the beneficial effects of linalool and geraniol, the major compounds of lavender (Lavandula angustifolia L.) and geranium (Pelargonium graveolens L'Hér. in Aiton) essential oils, on oxidative stress, inflammation, and iron metabolism of the rotenone and 6-hydroxydopamine-induced in vitro Parkinson's models. The experiments were carried out on all-trans retinoic acid differentiated SH-SY5Y cells. The effects of linalool and geraniol were compared to rasagiline, an MAO-B inhibitor. The results revealed that both essential oil compounds reduce the level of reactive oxygen species and alter the antioxidant capacity of the cells. They lower the secretion of IL-6, IL-8, and IL-1β pro-inflammatory cytokines. Moreover, linalool and geraniol change the expression of iron-related genes, such as the iron importer transferrin receptor 1, heme-oxygenase-1, and ferroportin iron exporter, and influence the intracellular iron contents. In addition, it has been unveiled that iron availability is concatenated with the actions of the essential oil compounds. Based on the results, linalool and geraniol are vigorous candidates as an alternative therapy for Parkinson's disease.

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REPORTED CUTANEOUS ALLERGIES TO ANTIMICROBIALS IN EUDRAVIGILANCE

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Background: Infectious diseases cause a global health burden and still millions of people die each year. In addition to antibiotic resistance, Adverse Drug Reactions (ADR) also pose significant challenges that affect therapy. EudraVigilance database collects, manages and analyses the reported, suspected ADRs.

Aims: The aim of the research is to provide a retrospective analysis on reported skin drug allergic reactions that occurred after the administration of antibacterial drugs. Furthermore, determining the frequency and strength of association between skin drug allergic reactions and each antibiotic agent. Finally, ascertaining the capability of pharmacological subgroups that cause cutaneous allergic drug reactions.

Methods: ADRs from the EudraVigilance database related to the active substances in ATCJ01 subgroup were analysed from 1st of January 2013 to 31st December 2022. MedDRA and DermNet® were used to filter out key terms related to skin drug allergic reactions. Besides the descriptive statistics, strength of associations were determined using Reporting Odds Ratio (ROR) with its 95% Confidence Interval (CI) and p-value.

Results: We obtained 170 APIs from 21 pharmacological subgroups, 339137 Individual Case Safety Reports, 995325 Reaction list PTs and from this 30783 were related to skin drug allergy accounting for 3.09%, of them 88.25% of reports were spontaneous and 45.71% were from the 18-64 age group, but 99.997% were from healthcare professionals. Related to allergy, 57.56% of cases were females, the highest was observed in glycopeptide group and the lowest was in the macrolide group, 64.34% and 52.77%, respectively. Penicillins were found to have the highest number of cases related to allergy with 8228 cases. But quinolones were found to have the strongest association to skin drug allergic reactions with ROR=4.95, 95%CI [4.54, 5.36] $p<0.0001$ and aminoglycosides with the weakest with ROR=0.33, 95%CI [0.25, 0.41] $p<0.0001$. Other medically important condition and caused/prolonged hospitalisation were the most frequently reported seriousness criteria 13675 and 10629, re-

spectively. However, life-threatening criterion showed the strongest association ROR=1.18, 95%CI [1.13, 1.22] p<0.0001. Despite the severity of the ADRs, results in death criterion had negative association with them ROR=0.84, 95%CI [0.79, 0.9] p<0.0001. Recovered/Resolved was the most significant outcome with 11318 (36.8%) reports and with positive association ROR=1.39, 95%CI [1.36, 1.41] p<0.0001. The ADRs related to allergies were found to have a negative association with fatal outcome ROR=0.86, 95%CI [0.79, 0.92] p<0.0001. Urticaria was the most frequent skin drug allergic reaction with 15259 (49.57%) of total cases, followed by angioedema 4522 (14.69%), Stevens-Johnson syndrome (SJS) 2953 (9.59%), toxic epidermal necrolysis (TEN) 2567 (8.34%) and acute generalized exanthematous pustulosis (AGEP) 1961 (6.37%). The following have shown strong associations with antibiotics for urticaria: quinolone ROR=6.43, 95%CI [5.94, 6.91] p<0.0001, for angioedema: quinolone ROR=4.52, 95%CI [3.53, 5.51] p<0.0001, for SJS: Other cephalosporins and penems ROR=4.2, 95%CI [3.06, 5.34] p<0.0001, for TEN: quinolone ROR=3.95, 95%CI [2.56, 5.34] p<0.0001, and for AGEP: streptogramin ROR=17.18, 95%CI [17.02, 17.34] p<0.0001.

Conclusion: We found quinolones to have the strongest positive association with the most common ADRs while the aminoglycosides the weakest ones and found women to be more prone to skin drug allergic reactions.

EVALUATION OF CYCLODEXTRIN UPTAKE VIA MACROPINOCYTOSIS IN MULTIDRUG RESISTANT CANCER CELLS

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Multidrug resistance (MDR) remains a significant obstacle in cancer chemotherapy and is often mediated by the overexpression of the efflux transporter P-glycoprotein (P-gp/MDR1). Cyclodextrins (CDs), cyclic oligosaccharides capable of forming inclusion complexes, have recently attracted attention as potential drug carriers and modulators of MDR. Their interaction with cellular membranes and their possible influence on drug accumulation through endocytic uptake make them promising candidates for addressing drug efflux-related limitations. In this study, the cellular uptake of cyclodextrins was investigated in drug-sensitive and multidrug-resistant cancer cell lines in order to evaluate their behavior in MDR-related settings.

Three paired cell models representing sensitive and multidrug-resistant phenotypes were used: NIH 3T3/NIH 3T3-MDR1, A2780/A2780-AD, and KB-3-1/KB-V1. Experimental measurements were performed by flow cytometry. First, MDR1 (P-glycoprotein, P-gp) expression and function were assessed by cell surface antibody labeling and calcein accumulation assays in order to confirm the MDR status of the selected cell lines. Second, the cellular uptake of fluorescently labeled cyclodextrins was evaluated using hydroxypropyl-β-cyclodextrin (FITC-HPBCD) and randomly methylated β-cyclodextrin (FITC-RAMEB), while FITC-dextran was used as a control. The experimental workflow included incubation of cell suspensions with FITC-labeled cyclodextrins, followed by washing, flow cytometric analysis, and data evaluation.

The results confirmed the MDR phenotype of the resistant models. Cell surface antibody labeling showed elevated P-gp expression in the multidrug-resistant cell lines compared with their corresponding sensitive counterparts. Calcein-AM accumulation assays also demonstrated significant P-gp activity, further validating the resistant phenotype in the selected models. These findings support the suitability of the applied cell pairs for studying the relationship between MDR status and cyclodextrin uptake.

Comparison of cyclodextrin uptake showed that FITC-HPBCD uptake was concentration-dependent across all examined cell lines. However, the pattern of uptake differed between the models. In the human cell pairs, FITC-HPBCD uptake was lower in KB-V1 and A2780-AD than in their sensitive counterparts, with reported P values of 0.0146 and 0.1286, respectively. In contrast, uptake in NIH 3T3-MDR1 appeared slightly higher than in NIH 3T3 cells, although this difference was not statistically significant. Overall, HPβCD uptake tended to decrease with the MDR phenotype in the human models, whereas the mouse NIH 3T3-MDR1 model showed a non-significant increase. This pattern indicates that cyclodextrin uptake behavior may depend on cell-specific endocytic mechanisms rather than on MDR phenotype alone.

In conclusion, significant P-gp activity and elevated surface expression in the resistant cell lines validated the MDR models used in this study. Cyclodextrin uptake was concentration-dependent in all cell lines, but the MDR phenotype did not correlate with increased uptake efficiency. Ongoing work aims to quantify the relationship between MDR levels and cyclodextrin internalization and to investigate the link between K-Ras signaling and P-glycoprotein-mediated drug resistance.

PREPARATION AND IN VITRO CHARACTERIZATION OF KETOPROFEN LOADED ELECTROSPUN EUDRAGIT-PVP NANOFIBERS FOR THE TREATMENT OF ORAL ULCERS

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Introduction: Oral ulcers are lesions that affect quality of life due to pain, inflammation, and discomfort. The use of conventional dosage forms in oral ulcer treatment is limited due to the short contact time resulting from the continuous salivary flow and mucosal mobility in the oral cavity (1). Ketoprofen (KET) is a BCS Class II drug with NSAID effects used in the treatment of oral ulcers, but its local efficacy is limited due to its pH-dependent limited solubility in an aqueous medium (2). Nanofibers are a good option for personalized drug delivery due to their high surface area and porosity, which increase drug solubility, improve retention time in relation to their mucoadhesive properties, and their adjustable size and doses.

Methods: Electrospun nanofibers were produced using a combination of Eudragit RL100/RS100 and polyvinylpyrrolidone (PVP K90; 2-4.8% w/w) with a total polymer concentration of 10-12% w/w. The characterization of nanofibers was done for their morphology, diameter and porosity (SEM/ImageJ), mechanical and mucoadhesive properties (Texture analyzer), KET loading capacity and in vitro release (UV-spectrophotometry), was conducted with dialysis membrane (50 mL pH 6.8 PBS, 37°C, 50 rpm). Kinetic modeling was evaluated via DDSolver. Cytotoxicity of formulations was evaluated by MTT test.

Results and Discussion: Despite the decrease in conductivity due to the addition of hydrophilic polymer and the increase in total polymer concentration, the increase in the viscosity of the polymer solutions resulted in achieving the spinnability required for nanofiber production and obtaining fibers with diameters of 551-603 nm and porosity of 42-61%.

The tensile strength was not affected with the increased amount of PVP in RS100 nanofibers, while RL100 nanofibers exhibited lower values. KET addition (loading capacity > 90%) significantly affected the viscosity, conductivity and tensile strength but had no effect on mucoadhesive properties. Formulations exhibited lower contact angle values with KET addition, which provided better wettability. In vitro release studies (> 80% release within 6 hr) provided an erosion-controlled profile. Both RL and RS nanofibers were shown to be non-cytotoxic.

Conclusion: Among the nanofibers, RL100:PVPK90 (6:4)-KET formulation offered promising results for oral ulcer treatment with appropriate morphological, mechanical and mucoadhesion properties, slower release and suitable cytotoxicity.

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FROM MECHANOCHEMISTRY TO LYOPHILISATION: PREPARATION-DEPENDENT BIOPHARMACEUTICAL PERFORMANCE OF MELOXICAM/CYCLODEXTRIN COMPLEXES

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Meloxicam (MLX) is a poorly soluble, selective cy-

clooxygenase-2 (COX-2) inhibitor widely used to treat chronic inflammatory conditions, including rheumatoid arthritis and osteoarthritis, and for postoperative pain management. Its low, pH-dependent solubility poses a major challenge in pharmaceutical formulation development, resulting in variable oral bioavailability and a delayed onset of therapeutic action.

Multiple strategies have been explored to enhance the aqueous solubility and dissolution rate of MLX, with cyclodextrin (CD) complexation emerging as a particularly promising approach. CDs are biocompatible cyclic oligosaccharides with a truncated-cone structure comprising a hydrophobic central cavity and a hydrophilic outer surface, enabling the formation of inclusion complexes with poorly soluble drugs. As a result, CD complexation can increase apparent solubility and dissolution rate, improve drug availability at the absorption site, and potentially enhance oral absorption while accelerating the onset of therapeutic action.

Various techniques are available for preparing solid-state inclusion complexes, and the selected approach must be tailored to the physicochemical properties of both the drug and the CD. In this study, mechanochemical activation by grinding was used as a rapid, solvent-free green chemistry approach to prepare MLX inclusion complexes with hydroxypropyl-β-cyclodextrin (HPβCD) at 1:1 and 1:2 molar ratios. In parallel, freeze-drying, a conventional solvent-based technique, was employed to enable simultaneous ammonium salt formation and CD complexation in a single formulation step. For that, MLX was dispersed in an aqueous HPβCD solution, followed by the addition of 10% (v/v) ammonia solution (pH 10.2) to ensure drug solubilisation prior to lyophilisation. Mechanochemical processing was performed at 30 Hz for 30 min. In all cases, the batch size was 1.5 g.

The obtained products were characterised using thermal (DSC and TG) and spectral (FTIR and XRPD) techniques to assess solid-state interactions. In vitro dissolution studies were conducted in simulated gastric (pH 1.2) and intestinal (pH 6.8) media without enzymes, while in vitro permeability was evaluated using biomimetic PermeaPad® membranes.

Lyophilisation yielded amorphous products comprising a mixture of MLX/HPβCD complexes and the MLX ammonium salt. In contrast, complexes prepared by grinding showed residual crystalline MLX, with lower residual crystallinity observed for the 1:2 complex. Conversion to the ammonium salt or grinding alone did not significantly enhance MLX dissolution, particularly at pH 1.2, whereas at pH 6.8 dissolution reached up to 65 % after 60 min. Prepared complexes exhibited markedly improved dissolution, especially at pH 6.8, where the complete drug dose dissolved within 5 min for lyophilised complexes and within 10 and 20 min for ground complexes at 1:1 and 1:2 ratios, respectively. The superior dissolution performance of the lyophilised systems is attributed to the synergistic effects of amorphisation, increased apparent solubility arising from ammonium salt formation, and MLX complexation with HPβCD. Importantly, neither complexation with HPβCD nor ammonium salt formation affected the inherently high in vitro permeability of MLX (Papp ≈ 2.5×10^{-5} cm s^{-1}).

Taken together, the enhanced MLX dissolution combined with preserved high permeability suggests that the prepared HPβCD complexes, particularly the lyophilised systems, have the potential to significantly improve oral bioavailability while enabling a faster onset of therapeutic action.

BRIDGING THE DIGITAL SKILLS GAP IN PHARMACY PRACTICE: OUTCOMES OF A TARGETED BLENDED LEARNING INTERVENTION FOR PRACTICING PHARMACISTS

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Background: The rapid digital transformation of modern healthcare systems demands advanced digital competencies from pharmacists to ensure effective patient-centered care, data security, and seamless interprofessional collaboration. Despite this growing urgency, structured continuing edu-

cation programs targeting digital health skills for practicing pharmacists remain highly fragmented. Consequently, significant gaps in digital proficiency persist across the European pharmaceutical workforce, highlighting a critical need for accessible, evidence-based upskilling initiatives.

Objectives: This study aimed to evaluate the real-world effectiveness of a modular, blended learning digital health training program on the self-reported competencies of practicing pharmacists. The intervention was implemented as part of the Romanian pilot of the EU-funded H-Pass (Health Professionals' and the DigitAl Team SkillS Advancement) project.

Methods: A single-group, pre-post educational evaluation design was employed. The study included practicing pharmacists from Bihor County, Romania, who participated in the H-PASS training program between May and July 2025. The blended learning model combined asynchronous e-learning modules with synchronous, trainer-facilitated onsite sessions. Competency shifts were measured using an 18-item self-reported questionnaire assessing three core domains: (1) Digital innovation and change management, (2) Communication and collaboration in digital healthcare, and (3) Data management and digital literacy. Statistical analyses included paired-samples t-tests, Cohen's d effect sizes, and internal consistency evaluations (Cronbach's alpha). Additionally, moderation and ceiling effect analyses were conducted using Python-based workflows to determine the influence of demographics and baseline proficiency on learning outcomes.

Results: A total of 84 pharmacists (89.3% female), representing a diverse range of age groups and professional experience, successfully completed the matched pre- and post-training evaluations. The intervention yielded statistically significant improvements across all three competency modules (all $p < 0.0001$), demonstrating large effect sizes ranging from $d = 1.04$ to 1.30. Post-training internal consistency of the instrument improved substantially (overall Cronbach's alpha = 0.74). At the item level, the most pronounced competency gains were observed in cultural competence in digital settings ($d = 0.86$), adaptive communication ($d = 0.85$), and data protection ethics ($d = 0.82$). Notably, training effectiveness was consistent across all demographic subsets; no significant moderating effects were found for age, gender, or years of professional experience, challenging the traditional 'digital native' assumption. Furthermore, a significant ceiling effect was identified ($r = –0.25$, $p = 0.02$), demonstrating that the curriculum rapidly accelerated the learning curve for novices, effectively narrowing the competency gap across the cohort. Finally, overall course satisfaction was high and served as a strong predictor of objective competency gains ($r = 0.528$, $p < 0.001$).

Conclusions: A structured, blended learning approach is a highly effective and scalable strategy for enhancing essential digital health competencies among practicing pharmacists. By successfully elevating proficiency regardless of age or prior experience, this training model ensures that the pharmaceutical workforce is equitably equipped to navigate the evolving digital healthcare landscape, ultimately fostering workforce resilience and improved patient care.

PHARMACOLOGICAL EVALUATION OF FLUORINE-CONTAINING CANNABIDIOL DERIVATIVES

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Introduction: Cannabinoids are extensively researched today due to their diverse pharmacological profiles. Among them, cannabidiol (CBD) and tetrahydrocannabinol (THC) are the most extensively studied. However, limited information is available regarding synthetically modified cannabinoids.

In this study, we investigated fluorine-substituted CBD derivatives (obtained from the Department of Pharmaceutical Chemistry, University of Debrecen), primarily focusing on their pharmacological properties in relation to the cardiovascular system. Fluorine is commonly incorporated into new drug molecules due to its ability to enhance potency and biological activity by altering the chemical nature of the molecules.

Methods: We assessed the cytotoxicity of these

derivatives using an MTT assay on H9c2 rat cardiomyocytes and evaluated their ability to protect cells from H_2O_2-induced oxidative stress. Antioxidant capacity was measured using FRAP, ORAC, ABTS, and CUPRAC assays. Additionally, we examined the cardioprotective potential of the compounds by pre-treating cells with the derivatives before exposure to doxorubicin, which is an anticancer agent with serious cardiotoxic side effects. We also performed experiments to analyze the effects of these substances on antioxidant protein levels using Western blot in two different conditions. Furthermore, we also investigated the activity of some of these molecules on h-ERG receptors, and the effect on H9c2 cells in simulated hypoxia-reoxygenation conditions.

Results: The IC_{50} values for the compounds were as follows: PFD14/A/I (0 μM), PFD14/B/I (60.53 μM), PFD43/I (57.63 μM), PFD17 (18.49 μM), PFD10/A/I (46.13 μM), PFD10/I/I (0 μM), and CBD (5.08 μM). Notably, the new derivatives exhibited slightly lower toxicity compared to the parent CBD molecule. Some derivatives effectively protected cells against H_2O_2-induced stress, with CBD demonstrating the most potent antioxidant activity, followed by PFD17. In doxorubicin-treated cells, several derivatives provided partial protection against cardiotoxicity. The fluorine-containing CBD derivatives exhibited great antioxidant and cytoprotective effects, with some outperforming the parent molecule in specific assays. Due to the Western blot results, some of the molecules can influence the levels of the antioxidant proteins (Nrf-2, CAT, HO-1), however, it is not enough to sustain the basic hypothesis as these proteins would protect the cells against the hypoxia-reoxygenation damage. These findings highlight their potential as promising candidates for further pharmacological research in the treatment of cardiovascular pathologies.

Conclusion: Taken together, our newly synthesized fluorine-containing compounds exhibit cytoprotective effects and considerable antioxidant potential. In certain aspects, they outperform the parent molecule. However, further investigations are needed, particularly in the fields of mitochondrial stress and different cell survival pathways (AKT/pAKT) .

DEVELOPMENT AND VALIDATION OF AN HPLC METHOD OF PIMECROLIMUS FOR DERMAL DELIVERY

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Pharmaceutical Technology and Drug Delivery

Pimecrolimus is a lipophilic macrolide lactone derivative and a selective calcineurin inhibitor widely utilized in the topical management of inflammatory skin disorders, particularly atopic dermatitis (1). Due to its complex structure and high lipophilicity, the accurate, rapid, and economical quantification of pimecrolimus remains a critical necessity in preformulation studies, and content uniformity processes. Although high-fidelity techniques like LC-MS/MS offer sensitivity, their operational complexity, high maintenance costs, and requirement for specialized personnel limit their sustainability for routine laboratory testing (2). Therefore, the primary objective of this study was to develop, optimize, and validate a simple, cost-effective, and reproducible high performance liquid chromatography (HPLC) method coupled with UV detection for the reliable quantification of pimecrolimus for dermal drug delivery in compliance with international guidelines.

Chromatographic separation was achieved using an Agilent 1100 Series HPLC system equipped with a UV detector, a gradient pump, and a column compartment. A C18 column (4.6 mm x150 mm, 5 μm, InertSustain, GL Sciences, Japan) was utilized to optimize peak symmetry and column efficiency. The mobile phase composition was systematically optimized to resolve potential baseline noise. The final eluent consisted of a mixture of acetonitrile and 0.1% phosphoric acid in a ratio of 75:25. The flow rate was maintained at 1.1 mL/min with a sample injection volume of 50 μL and the column temperature was equilibrated at 60°C. The target analyte was monitored at an optimized single UV wavelength of 215 nm. Method validation was thoroughly conducted according to the International Council for Harmonization (ICH) Q2(R1/R2)

guidelines, evaluating parameters including linearity, specificity, precision, accuracy, robustness, limits of detection (LOD), and quantification (LOQ).

Under the optimized chromatographic conditions, pimecrolimus eluted as a sharp, symmetrical peak with a reproducible retention time of approximately 8 minutes, showing no interference from the mobile phase matrix or common excipients, thereby confirming the method's high specificity. The calibration curve displayed excellent linearity over a concentration range of 2.5-125 μg/mL with a correlation coefficient R2 > 0.9999, indicating a proportional correlation between peak area and concentration. Accuracy studies yielded a mean recovery rate between 99.4% and 103.2% across three distinct quality control levels, demonstrating negligible systemic bias. Assessments revealed relative standard deviations well below the strict threshold of 2% for both intraday repeatability and interday/inter-analyst intermediate precision, validating the method's robust reproducibility. Robustness testing indicated that minor deliberate variations in flow rate, column temperature, or mobile phase ratio did not critically alter the quantitative results. The calculated LOD and LOQ values were 0.352 μg/mL and 1.064 μg/mL respectively, illustrating high sensitivity.

A simple and validated HPLC method was successfully established for pimecrolimus. By eliminating the necessity for complex extraction protocols, aggressive solvents, or specialized mass detectors, this method offers a practical, fast, and economical analytical platform.

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INVESTIGATION OF MYD88 INHIBITION BY SIRNA-MEDIATED GENE SILENCING IN A MACROPHAGE MODEL

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The adaptor protein MyD88 is a central mediator of innate immune signaling downstream of Toll-like receptors (TLRs), linking pathogen recognition to the activation of inflammatory pathways. Dysregulated MyD88 signaling has been implicated in chronic inflammatory diseases, infections, and malignancies, making it an attractive therapeutic target.

This study aimed to investigate the effects of MyD88 inhibition using siRNA-mediated gene silencing in M1-polarized macrophages differentiated from THP-1 monocytes. siRNA delivery was achieved using Lipofectamine-based transfection.

Gene silencing efficiency was confirmed by quantitative PCR (qPCR), showing a substantial reduction of MYD88 mRNA levels to approximately 10–20% of control levels. Functional consequences were assessed by measuring inflammatory mediators using ELISA. MyD88 silencing resulted in a pronounced decrease in TNF-α expression and a moderate reduction in IL-6 levels compared to Lipofectamine-treated controls. Additionally, IFNγR2 expression was reduced following MyD88 knockdown, suggesting altered interferon signaling. Notably, Lipofectamine treatment alone induced a marked increase in IL-1β expression, whereas MyD88 silencing only partially attenuated this response, suggesting the involvement of MyD88-independent or transfection-associated inflammatory pathways.

In conclusion, MyD88 inhibition effectively modulates key inflammatory pathways in macrophages, particularly affecting TNF-α and IL-6 production, supporting its potential as a therapeutic target in inflammatory diseases.

ESKETAMINE-INDUCED GAMMA-DELTA SHIFT AS A POTENTIAL EEG MARKER OF RAPID ANTIDEPRESSANT ACTION

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Subanaesthetic racemic ketamine exerts rapid antidepressant effects that have been associated with

characteristic quantitative electroencephalographic (qEEG) changes, including a temporal transition between gamma and delta activity, which we have termed the gamma-delta shift phenomenon. However, the contribution of the individual ketamine enantiomers to this phenomenon remains unclear, as does its specificity to rapid-acting antidepressant effects. Therefore, we investigated the dose-dependent effects of esketamine and arketamine on the gamma-delta shift and compared them with those of the conventional selective serotonin reuptake inhibitor escitalopram. In addition, the antidepressant-like activity of the ketamine enantiomers was evaluated in a chronic restraint stress model of depression in Wistar rats.

Fronto-parietal EEG recordings were performed following intraperitoneal administration of esketamine (7.5, 15, or 30 mg/kg), arketamine (7.5, 15, or 30 mg/kg), escitalopram (2 or 10 mg/kg), or vehicle (saline, 1 mL/kg) at the beginning of the passive phase. The gamma-delta shift was defined as an increase in EEG gamma power during wakefulness followed by enhanced EEG delta power during non-REM sleep. In a separate group of chronically stressed rats, the antidepressant-like activity of the two ketamine enantiomers was compared in the forced swimming test following administration of 15 mg/kg esketamine, 15 mg/kg arketamine, or vehicle.

Esketamine induced the gamma-delta shift phenomenon in a dose-dependent manner. While the lowest dose (7.5 mg/kg) did not induce the phenomenon, administration of 15 mg/kg resulted in elevated gamma power during wakefulness followed by a rebound elevation of delta power during non-REM sleep. This effect was more pronounced at 30 mg/kg, with robust gamma enhancement followed by increased non-REM delta power. In contrast, arketamine failed to induce a gamma-delta shift at any of the tested doses, although moderate elevations in gamma activity were observed at higher doses. Similarly, escitalopram did not produce the gamma-delta shift at either 2 or 10 mg/kg. In chronically stressed rats, esketamine (15 mg/kg) significantly reduced immobility time in the forced swimming test, whereas arketamine at the same dose produced no significant antidepressant-like effect.

These findings demonstrate that the gamma-delta shift is selectively induced by esketamine, but not by arketamine or the conventional SSRI escitalopram, and parallels the antidepressant-like efficacy of the ketamine enantiomers. The absence of this phenomenon following escitalopram further suggests that the gamma-delta shift may be associated with mechanisms specific to rapid-acting antidepressants. Further studies are needed to establish the potential of the gamma-delta shift phenomenon as a qEEG biomarker of rapid-acting antidepressant effects.

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FORMULATION CONSIDERATIONS FOR DIRECT COMPRESSION OF ORALLY DISINTEGRATING TABLETS

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In the manufacture of quickly disintegrating, orodispersible tablets a few different production technologies are available: moulding, freeze-drying and even three-dimensional (3D) printing. Each technology has certain advantages, but among these approaches, direct compression is the most cost-effective. To directly compress (DC) powders into orally disintegrating tablets (ODTs) some key characteristic requirements need to be fulfilled which otherwise would only be attainable with preceding granulation steps.

Excipient manufacturers offer a variety of suitable fillers, which are deliberately designed to align with these requirements and the intended use of the medicine. The DC procedure is simple: only a mixing stage with the active ingredient(s) and additional excipients, like lubricants, is necessary. The selection of the ideal option for our purposes needs consideration of both the manufacturing and patient-related factors: in addition to technological processing aspects, potential incompatibilities, palatability and sugar-sensitivity are also decisive.

We have compared four different marketed co-processed (spray-dried) lactose-based excipients and their corresponding physical mixtures (PMs) to prove and measure better powder performance and assess the qualities in manufacturing ODTs. Results have shown differences between starch and cellulose containing excipients in powder properties and the resulting tablet behaviour as well. StarLac® had an excellent, 7,85 g/s powder flow rate in comparison to 4 to 5 g/s in the other

excipients and practically no flow of the PMs. The differences between the tablets compressed with each of the three lubricants included were much less considerable a seen across the fillers themselves –this is consonant with the claims of the manufacturer which say their co-processed excipients (CPEs) have reduced sensitivity to lubricants.

Spray drying effectively improves physical attributes of the materials which is apparent from the results compared to the PMs. We found that some PM were hardly or not at all applicable for the compression of tablets, whereas the spray-dried materials functioned well. All tablets made of CPEs complied with pharmacopoeial regulations of the disintegration time, however, after performing an accelerated stability test, we found slight or large increases in different batches. While starch containing CPEs (CombiLac® and StarLac®) and corresponding PM had an average of 27,7 s, cellulose containing tablets (MicroceLac® and Cellactose®) disintegrated in an average of 12,2 s with one exception of the CT (Cellactose® modelling) PM which had 163 s average disintegration time. Besides the assessed features, in real-life drug development other aspects should also be considered such as the mouthfeel or the taste masking ability of the filler which would differ with the cellulose or starch content of the CPEs. Based on the results we could determine key differences of the examined CPEs and were able to prove the benefits of employing these novel spray dried fillers in manufacturing ODTs.

CYTOTOXICITY AND CELL LINE STUDIES OF CHITOSAN ASCORBATE BUCCAL FILMS CONTAINING CAPTOPRIL

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Buccal films have attracted continued interest due to their several advantages. However, developing effective buccal films for hydrophilic drugs remains challenging due to limited buccal permeability. Captopril (CAP), a watersoluble ACEI, represents a suitable model for evaluating buccal films. Chitosan–ascorbate (CHI-AA) has previously been studied in solution for its cytotoxicity and permeation-enhancing properties. However, its performance as a buccal film dosage form requires further investigation. Therefore, the present study was carried out to evaluate the cytotoxicity, permeability and stability of the previous developed CHI-AA-based buccal films loaded with CAP [1] in order to further define the performance and limitations of this dosage-form system.

Medium molecular weight CHI was used as film-forming polymers. Glycerol (GLY) was added to the film as a plasticizer. Ascorbic acid (AA) was added to the film to dissolve CHI and enhance permeation. CAP was used as an active agent. Acetic acid (Ac) provided an appropriate acidic media for CHI dissolution during the preparation of the reference films. Mucin (Type II) dispersion was used in the in vitro mucoadhesion test. Films were prepared employing the solvent casting method. The different amount of CHI was dispersed in the acidic aqueous solution and mixed until complete dispersion. After a clear solution was formed, the CAP was added and mixed. The calculated amount of plasticizer, based on the dry weight of the polymer, was then added to the solution and stirred for 20 minutes. A predetermined amount of the solution was poured onto plastic Petri dishes and allowed to dry in a ventilated oven under predetermined conditions. Blank and CAP-loaded films were assessed. Cytotoxicity and permeability were evaluated using TR146 cells and compared with CHI-Ac films as a reference. Accelerated stability test (40 °C/75% RH, three months) was performed to monitor moisture content, mechanical properties, mucoadhesion force, and drug content. FT-IR spectroscopy was used to investigate potential chemical interactions.

The in vitro cytotoxicity results confirmed that the formulated films are well tolerated by TR146 cells, exhibiting cell viability over 80% in the case of all samples, highlighting the low toxicity and a good safety profile. The permeability test demonstrated that the CHI-AA films significantly enhanced the buccal permeation of the CAP compared to the CHI-Ac films by tenfold. Stability investigations under accelerated storage conditions revealed that the films undergo progressive moisture uptake over time, leading to changes in thick-

ness, mechanical properties, mucoadhesive force, and a decrease in CAP content after 3 months, but they were able to retain almost all of their active ingredient content (>90%) after 60 days. However, FT-IR spectroscopy indicated that the observed changes were mainly physical and moisture-induced, with no significant decomposition or structure changes.

Overall, the findings of this work provide an in vitro, dosage-form–level characterization of CHI-AA buccal films, and highlight their cytocompatibility, and permeability-enhancing potential.

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THERAPEUTIC DRUG MONITORING-GUIDED HIGH-DOSE LINEZOLID IN PAEDIATRIC VRE MENINGITIS: A CASE REPORT

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Background: Central nervous system (CNS) infections caused by vancomycin-resistant Enterococcus faecium (VRE) present a therapeutic challenge, particularly in paediatric patients. Intravenous linezolid is a key treatment option; however, its optimal dosing in CNS infections remains uncertain, and therapeutic drug monitoring (TDM) may be required.

Case description: We report the case of a 3-year-old male (15 kg) admitted following severe traumatic brain injury with complex craniofacial fractures and subsequent neurosurgical interventions. The clinical course was complicated by meningitis. Cerebrospinal fluid (CSF) cultures repeatedly yielded vancomycin-resistant Enterococcus faecium with a minimum inhibitory concentration (MIC) <4 mg/mL. In the absence of an exact MIC value, we calculated using the most common MIC value of 2 mg/ml.Initial antimicrobial therapy included meropenem and vancomycin; however, due to VRE isolation, treatment was switched to linezolid at a guideline-recommended dose (10 mg/kg/dose every 8 hours).

Intervention: Due to concerns regarding CNS penetration and clinical response, linezolid therapy was guided by TDM from both serum and cerebrospinal fluid (CSF). Linezolid is an exposure-dependent antibiotic, the pharmacokinetic/pharmacodynamic (PK/PD) target is defined as an area under the unbound concentration-time curve over 24 hours to the pathogen's MIC ratio of 80-120 mg*h/L (AUC24/MIC = 80-120 mg*h/L). The risk of thrombocytopenia as a common side-effect increases with daily linezolid exposure AUC24 >300 mg*h/L. During treatment serum and CSF concentrations were measured by using high performance liquid chromatography with ultraviolet detection (HPLC-UV). Initial drug exposure (150 mg every 8 hours) proved subtherapeutic. Based on measured concentrations, stepwise dose escalation was performed up to 1200 mg/day (approximately 2.67-fold higher than the initial weight-based daily dose). CSF/serum linezolid ratio was 0,4 on the 6th day of therapy (dose: 600 mg/24h, serum: 5,21 mg/L, CSF: 2,1 mg/L, AUC24: 125 mg*h/L, AUC24/MIC: 62,5 mg*h/L), 0.65 on day 8 (dose: 1200 mg/24h, serum: 8.37 mg/L, CSF: 5.45 mg/L, AUC24: 200 mg*h/L, AUC24/MIC: 100 mg*h/L) which increased to 0.78 (dose: 1200 mg/24h , serum: 13.5 mg/L, CSF: 10.6 mg/L, AUC24: 324 mg*h/L, AUC24/MIC: 162 mg*h/L) by day 19. Due to the high AUC24 value, the dose was reduced. Therapy was completed on the 26th day.

Outcome: Subsequent microbiological samples from CSF and surgical sites became negative, and no brain abscess was confirmed. The patient underwent ventriculoperitoneal shunt placement, and linezolid therapy was successfully completed. No treatment-related adverse effects were observed during therapy.

Conclusion: This case highlights that standard linezolid dosing may be insufficient in paediatric CNS infections caused by VRE. These results suggest that linezolid levels in both blood and cerebrospinal fluid are dose- and time-dependent. TDM-guided dose optimisation may be essential to achieve adequate CSF exposure and favourable clinical outcomes.

ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF VESATOLIMOD BY HPLC

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Introduction: Vesatolimod (GS-9620), 4-amino-2-butoxy-8-{[3-(pyrrolidin-1 ylmethyl)phenyl] methyl}-5,7-dihydro-pteridin-6-one, is an orally active, selective Toll-like receptor 7 (TLR7) agonist developed for the treatment of chronic viral infections. It exerts its therapeutic effect by activating the body's innate immune response through specific pathways. Its most prominent effect is the stimulation of type I interferon (IFN-α, etc.) production. It indirectly enhances the effector functions of natural killer (NK) cells and antigen-specific CD8+ T cells (1). In drug development processes and quality control stages for biotechnological products, the development of reliable analytical methods for quantifying the active ingredient is critical. In our study, we aim to validate an HPLC method for the quantification of Vesatolimod.

Materials and Method: Analytical method development studies were carried out using a reverse-phase HPLC system (Agilent 1100 Series HPLC). The column is a Phenomenex Jupiter C18 Column (150 mm × 4.6 mm, 5 μm) and the temperature is 30 °C. Mobil phase is a two component: A: Water containing 0.1% formic acid, B: 100% methanol. 0-2 min interval: 95:5, 2-10 min ramp 70:30, and 10-12 min interval back start conditions. Flow rate is 1.0 mL/min, injection volume is 10 μL, wavelength is 282 nm, and run time is 12 min. For method calibration, a 100 μg/mL Vesatolimod stock solution was prepared, and standard solutions at concentrations of 10, 20, 30, 40, 50, and 60 μg/mL were prepared by dilution. Linearity, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ), and stability (24 and 48 hours at room temperature) were evaluated, and the validation process was performed in accordance with ICH Q2(R1) guidelines.

Results and Discussion: The chromatographic retention time of Vesatolimod was 4.63 min. No interventions were observed with the Vesatolimod peak. The linear regression equation for the calibration curve was $y = 0.2723x + 0.0947$, with an R^2 of 0.9997, over the range of 10–60 μg/mL. Plasma recovery of Vesatolimod at 50 ppm was calculated for 6 samples. Intra and inter-day %RSD values are ≤ 2.0. LOD is 0.272 μg/mL, LOQ is 0.899 μg/mL.

Conclusion: The developed HPLC method demonstrates high precision, accuracy, and sensitivity, providing a guide for the quantitative determination of Vesatolimod. This approach offers a comprehensive dataset for analytical quality control in future preclinical and clinical studies.

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DEVELOPMENT AND VALIDATION OF A HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY METHOD FOR NINTEDANIB

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Introduction: Nintedanib (ND), methyl (3Z)-3-[[4-[methyl-[2-(4-methyl piperazine-1-yl)acetyl]amino] anilino]-phenylmethylidene]-2-oxo-1H-indole-6-carboxylate, is an indolinone derivative small molecule that potently blocks vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) receptors, also classified in the literature as a triple angiokinase inhibitor (1, 2). ND is used clinically for the treatment of idiopathic pulmonary fibrosis (IPF) (3). In this study, we present a simple, accurate, and sensitive HPLC method for determining the amount of (ND) in mouse plasma samples.

Materials and Methods: The mobile phase used was acetonitrile:0.1% trifluoroacetic:water (35:20:45) at a flow rate of 1 mL/min, with a wavelength of 392 nm. The separation was carried out using a C18 column (125mm × 4.6mm × 3.5μm). Standard solutions at concentrations of 0.2, 0.4, 0.5, 0.6, 0.8, 1, 1.5, 2, 3, 5, 6, 7, and 8 μg/mL for ND were prepared and evaluated. The proposed method has been statistically validated in accordance with ICH guidelines for linearity, accuracy, precision, specificity, limit of detection (LOD), and limit of quantification (LOQ).

Results and Discussion: This method showed linearity that obeys the Beer-Lambert law over a concentration range of 0.2 - 8 μg/mL for ND The chromatographic retention time of ND was 4.65 min. The linear regression equation for the calibration curve was y = 38.551x – 0.3946, with an R2 value of 0.9992, indicating good linearity. The method was validated, with results well within the limit of accuracy (100±2) and %RSD within 2. No interventions were observed with the ND peak. The LOD and LOQ values were determined to be 0.5 μg/mL and 1.4 μg/mL, respectively.

Conclusion: The above method was successfully developed and validated for the quantitative routine analysis of ND in plasma samples. This study thus exploits the potential to obtain pharmacokinetic data for ND, which may be required in future preclinical and clinical studies.

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PATIENT-CENTERED PHARMACEUTICAL DEVELOPMENT AND CLINICAL TRIALS: PATIENT RECRUITMENT AND RETENTION

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Background: Clinical research represents the evidentiary foundation of medical innovation and public health protection; however, patient recruitment and retention remain among the most persistent operational challenges in clinical trial conduct. Delays in enrollment and premature participant withdrawal may compromise external validity, prolong study timelines, and increase development costs. Recruitment difficulties arise from a complex interaction of patient-related, investigator-related, and logistical factors. Limited health literacy, perceived risk, mistrust toward research, protocol complexity, administrative burden, and infrastructural constraints may all negatively influence participation willingness and long-term engagement in clinical studies.

Objectives: The aim of this work is to investigate the motivational factors, attitudes, and decision-making mechanisms influencing patient recruitment and retention in clinical trials from a patient-centered perspective. The research integrates three stakeholder perspectives: physician motivations and willingness to involve patients in clinical studies, the participation and retention motivations of clinical trial subjects, and the attitudes of the general patient population attending the clinics of the University of Szeged toward clinical research participation.

Methods: This study employs structured questionnaires administered to physicians, current clinical trial participants, and members of the general patient population. Quantitative and qualitative evaluation enables the identification and segmentation of motivational drivers, behavioral determinants, trust-related factors, and knowledge gaps associated with clinical trial participation. The study further investigates operational and communication-related barriers affecting recruitment and retention processes.

Expected Results: The study is expected to identify key physician- and patient-related determinants affecting recruitment efficiency and participant retention, as well as societal attitudes toward clinical research. Based on the findings, ethically compliant, non-financial motivation strategies may be developed for investigators and investigational sites, accompanied by patient-centered educational and communication materials designed to improve public awareness and acceptance of clinical research. Improved communication, targeted motivational strategies, and patient-centered trial design are anticipated to contribute to enhanced recruitment efficiency, improved repre-

sentativeness, and greater operational predictability in clinical trials.

Conclusion: The integration of patient-centered and investigator-centered perspectives may provide a more comprehensive framework for optimizing recruitment and retention strategies in clinical trials. Improved understanding of motivational and behavioral determinants could contribute to enhanced operational feasibility, increased participant representativeness, and more sustainable clinical research processes.

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IN VIVO EVALUATION OF MALEIC ACID MODIFIED CHITOSAN FOR OCULAR DELIVERY: PROOF OF CONCEPT

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The aim was to develop a polymer conjugate named chitosan-maleic acid (CS-MA) wit enhanced mucoadhesiveness and activityagainst Escherichia coli. Therefore, chitosan (CS) and maleic acid (MA) were conjugated via formation of amide bond. Characterization via proton nuclear magnetic and infrared spectroscopy was carried out and attache maleic acid groups were quantified by free amino groups assay [1]. Biocompatibility of conjugate was assessed following resazurin assay on fibroblasts, membrane damage on human erythrocytes and Hen's Egg-Chorioallantoic membrane tests. Polymers were characterized in terms of swelling behavior, pH, hardness, in vitro drug release and disintegration. To test mucoadhesive properties of CS-MA polymer, rheometer, rotating cylinder, inclined plane, and texture analyzer were the instruments utilized. Furthermore, antibacterial efficacy of the conjugate was established by direct agar diffusion method and in vivo test was carried out to determine tolerability of the modified polymer. Results exhibited successful synthesis of the biomaterial, maintaining the great biocompatibility of native chitosan even though a 68.81% of modification was achieved. Additionally, mucoadhesive studies showed improved properties of CS-MA compared to native polymer, with 2.42-fold, 4-fold, 3.42-fold and 4.05-fold increase in dynamic viscosity, retention time, overall attachment work and peak force of detachment, respectively. Finally, antibacterial activity was enhanced in 1.77-fold and in vivo experiments showed no irritation and good tolerability of CS-MA polymeric conjugate. In conclusion, CS-MA effectively developed exhibiting promising features capable of revolutionizing the polymeric field.

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PRESYNAPTIC MODULATION OF GLUTAMATERGIC AND MONOAMINERGIC NEUROTRANSMISSION BY DEXTROMETHORPHAN IN ISOLATED RAT BRAIN SYNAPTOSOMES

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Introduction

Dextromethorphan (DXM) is a widely used antitussive drug with a complex neuropharmacological profile that includes NMDA receptor antagonism, sigma-1 receptor activity and interactions with monoaminergic neurotransmission. Renewed interest in DXM has followed the introduction of dextromethorphan-containing combinations for neuropsychiatric indications; however, its direct effects on presynaptic neurotransmitter machineries remain insufficiently characterized.

Aim

The aim of the present study was to investigate the effects of DXM on presynaptic glutamate release, monoamine uptake and monoamine oxidase (MAO) activity using isolated rat brain synaptosomes and complementary in vitro assays.

Methods

Presynaptic glutamate release was assessed in rat

brain synaptosomes using an enzyme-coupled fluorometric detection system. Synaptosomal depolarization was induced by 4-aminopyridine. Monoamine transporter function was examined using a fluorescent transporter substrate, ASP^+. In parallel, the effects of DXM on MAO-A and MAO-B activity were determined in enzyme activity assays over a broad concentration range.

Results

DXM produced a non-conventional concentration–response relationship on glutamate release. Exposure to concentrations ranging from 1 nM to 10 μM resulted in an increase in extracellular glutamate compared with control conditions, whereas this facilitatory effect progressively diminished at higher concentrations. At 100 μM, glutamate levels approached or fell below those observed in untreated controls, indicating a reversal of the response with increasing DXM exposure. A different concentration range was required to affect monoamine uptake: ASP^+ accumulation remained largely unchanged at lower concentrations, while 400 and 800 μM DXM significantly reduced transporter-mediated uptake. DXM also decreased the activity of both MAO-A and MAO-B. This effect was detectable from the low micromolar range and showed no pronounced preference for either isoenzyme.

Conclusion

These findings demonstrate that DXM directly modifies several presynaptic processes and that these effects occur within markedly different concentration ranges. In particular, the non-monotonic modulation of glutamate release suggests a mechanism more complex than a simple consequence of NMDA receptor blockade. The distinct concentration dependence of glutamatergic, transporter-related and MAO-associated effects further supports the multimodal nature of DXM pharmacology. Characterization of these presynaptic actions may contribute to a better understanding of the mechanisms underlying the central nervous system effects of dextromethorphan and provides a basis for further mechanistic comparison with other glutamatergic modulators.

NEURAMINIDASE INHIBITOR-BASED HYDROPHOBIC TAGS

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Neuraminidase inhibitors (NIs) are the most prominent antivirals available against influenza infections: by occupying the binding pocket of influenza neuraminidase, they inhibit the release of viral particles from infected cells, slowing the spread of the virus between cells. Due to genetic drift and shift, resistance against NIs can develop spontaneously, necessitating the need for the development of novel antivirals and the improvement of currently available drugs [1]. The purpose of our work is the development of targeted influenza neuraminidase degraders based on the two globally approved NIs zanamivir and oseltamivir.

Targeted protein degradation is an exciting approach in small molecule drug design which hijacks the cell machinery to induce the proteolysis of specific proteins of interest (POIs). About a dozen different modalities are known by now, some with clinical validation (e.g. the PROTAC vepdegestrant, or the molecular glue pomalidomide), and each coming with its own scope and limitations [2]. A less commonly used, but very promising approach is hydrophobic tagging (HyTag), which mimics the misfolding or denaturation of POIs to induce their degradation. By connecting a POI ligand with a compact hydrophobic group, such as adamantane, the hydrophobic surface area of the POI is increased, which the cell recognizes as damage, setting the protein up for degradation. This approach is especially well suited for polar ligands (such as the extremely polar zanamivir), unlike the more popular PROTAC approach, which generally requires POI ligands of lower polarity for efficacy [3].

The focus of this work is the modular synthesis of NI-adamantane-conjugates, with the two parts being connected in two different positions by linkers of various sizes and rigidity, in order to generate a molecular library for later biological studies.

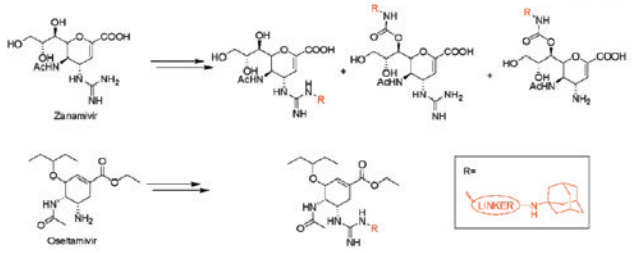


Figure 1. Synthesis of zanamivir- and oseltamivir-based HyTags targeting influenza neuraminidase

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1. J. Xu, Q. Luo, Emerg. Microbes Infect. ***2024****, 13, (1), 2429627*

GLOBAL AND NATIONAL TRENDS IN HUMAN CLINICAL TRIALS: FOCUS ON HUNGARY

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Background: Human clinical trials play a central continuous role in the development of new pharmaceuticals, medical devices, and therapeutic interventions, while also exerting significant scientific and economic impact. Over the past two decades, the number of clinical trials has increased globally. According to the WHO and ClinicalTrials.gov globally, tens of thousands of clinical trials are registered each year. In 2024, this number was estimated to be 30.000-40.000. In recent years significant changes have occurred in the geographical distribution and initiation volume of clinical trials.

Objectives: The aim of this study was to analyze current global and national trends in human clinical trials, with particular emphasis on differences between commercial (industry-sponsored or sponsor-initiated) and non-commercial (academic or investigator-initiated) studies, as well as to assess Hungary's position in the global clinical research landscape.

Methods: Data from the publicly accessible ClinicalTrials.gov database was analyzed between the 1st of January 2014 and 27th of May 2025. Trials were categorized by sponsor type (commercial vs. non-commercial) and geographic location, with a specific focus on Hungary. Disease-specific analyses were conducted from 2014 onward using 30 predefined therapeutic area keywords, restricted to commercially sponsored trials. The relative contribution of each therapeutic area was evaluated against the total number of globally initiated sponsored trials.

Results and discussion: Globally, the number of clinical trials continued to increase; however, a marked geographical shift toward Asia has been observed, which may be driven by cost advantages, regulatory characteristics, and demographic factors. In parallel, Europe's relative share declined. Hungary's contribution to global clinical trials decreased from 1.27% in 2014 to 0.49% in 2024. The vast majority of trials were commercially sponsored (ca. 92%), while the proportion of non-commercial studies remained very low (ca. 0.12%), likely reflecting limitations in registry classification. In Hungary, trends in sponsored clinical trials were analyzed across the four major university medical centers. A decline was observed between 2015 and 2024 of 5% to 50%. Based on global distribution,18 therapeutic areas, each representing more than 1% relative share together, accounted for 96.1% of all sponsored trials worldwide. In Hungary, 17 such key therapeutic areas were identified, representing 95.8% of sponsored trial activity and showing a high degree of alignment with global therapeutic areas. In most of these areas, a decline in commercially sponsored clinical trials was observed, consistent with national trends. This decrease was particularly pronounced in oncology, cardiovascular, and diabetes-related studies, while it was less evident in ophthalmology and neurology. The proportion of Phase I trials in Hungary remained consistently low, averaging approximately 5% annually, compared to nearly 20% in Belgium and 27% in the United States.

Conclusion: Hungary's clinical research competitiveness has declined over the past decade within a dynamically evolving global environment. Limited early-phase infrastructure, a complex and multi-layered regulatory framework, and constraints in human resource capacity are likely contributing factors. Improving competitiveness will likely require development of early-phase clinical infrastructure, increased efficiency of regulatory and administrative processes, strengthening of human resources, and the promotion of academic clinical research. Targeted improvements in these areas are essential to enhance Hungary's position in the global clinical research landscape.

INSIGHTS INTO THE KINETIC PROPERTIES OF [3H]ASEM BINDING TO A7 NACH RECEPTORS

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Introduction: The α7 nicotinic acetylcholine receptor (nAChR) is a key pharmacological target in neurological processes. Although positive allosteric modulators (PAMs) have gained increasing attention, their binding characteristics remain incompletely understood. Radioligands are available only for the orthosteric binding site with [11C] ASEM most widely used in human PET studies. Kinetic binding studies are particularly valuable, since they provide mechanistic insight into how fast a ligand binds (kon) and how long it stays bound (koff).

Aims: Our aim was to characterize first the in vitro binding kinetics of [^{3}H]ASEM to human α7 nicotinic acetylcholine receptor and to determine the key kinetic parameters (Kd, koff, kon, t1/2).

Method: Membrane homogenates were prepared from Flp-In 293 cells stably expressing recombinant α7 nACh subunits forming functional homopentameric ion channels. Binding assays were performed at 25 °C using the orthosteric antagonist radioligand [^{3}H]ASEM. Non-specific binding was defined in the presence of 10 μM methyllycaconitine (MLA), and PAMs were applied as pretreatment when required. Association kinetics were assessed over varying incubation times, while dissociation was initiated by excess MLA. Samples were filtered over UniFilter® GF/C, and radioactivity was quantified using a microplate counter.

Results: Kinetic binding analysis of [^{3}H]ASEM at α7 nACh receptors revealed a dissociation rate constant (koff) of 0.462 min^{-1} and an association rate constant (kon) of 1.0785 $nM^{-1}{\cdot}min^{-1}$, corresponding to a dissociation half-life (t1/2) of 1.57 min. These parameters indicate relatively rapid binding kinetics. The equilibrium dissociation constant (Kd) derived from kinetic parameters (koff/kon) was 0.428 nM, while the experimentally determined Kd from equilibrium binding was 0.5654 nM. We began to investigate the effect of a PAM compound (BNC-375) which did not affect the dissociation kinetics of [^{3}H]ASEM.

Conclusion: We determined the kinetic parameters of [^{3}H]ASEM binding at α7 nACh receptor. BNC-375 did not affect [^{3}H]ASEM dissociation kinetics. In addition to the investigation of α7 nACh receptor allosteric modulators, particularly PAMs, which are of significant interest for therapeutic development, we plan to extend these kinetic investigations to agonist radioligand for a more comprehensive assessment of PAMs receptor binding.

QUALITY ASSURANCE CHALLENGES IN THE ESTABLISHMENT OF A CAR-T CENTER – PREPARATION FOR THE 2027 SOHO REGULATION

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Introduction: CAR-T cell therapy represents one of the most significant innovations in personalized oncohematological treatments; however, it requires a complex, multi-level integrated quality assurance system throughout the entire patient pathway. The collection, processing, and clinical application of cellular products take place at the intersection of different regulatory frameworks—primarily SoHO and ATMP—resulting in unique operational and compliance challenges.

Objective: The aim of this presentation is to demonstrate the requirements and challenges posed by the new SoHO regulation, applicable from 2027, in the establishment and operation of CAR-T centers, with particular emphasis on quality assurance systems and patient safety. Methods: The new European Union SoHO (Substances of Human Origin) regulation, expected to be fully applicable from 2027, introduces significant changes in the regulation of substances of human origin, including CAR-T cells. This work is based on the review and analysis of relevant legal provisions. As a result, an overview of the current European regulatory environment—particularly the SoHO regulation and the ATMP framework—as well as a summary of the quality assurance aspects of CAR-T therapeutic practice, is provided.

Results and Discussion: The SoHO regulation introduces an unified, risk-based regulatory model covering the entire chain from donor to process-

ing to clinical use. Consequently, significant changes will be required in the operation of hematology and CAR-T centers, particularly in the development of traceability systems, the expansion of biovigilance, and the tightening of documentation and audit requirements. In addition, the transformation of quality management systems and the redefinition of institutional and regulatory roles are essential. A key challenge lies in managing the interface between SoHO and ATMP regulations, which results in dual compliance obligations.

Conclusion: The introduction of CAR-T therapy necessitates a new type of integrated regulatory and quality management approach. The combined application of SoHO and ATMP frameworks requires extensive, multidisciplinary collaboration at both institutional and regulatory levels. The key to future success lies in the development of flexible, adaptive quality assurance systems capable of addressing the regulatory and clinical challenges arising from rapidly evolving cell-based therapies.

BRIDGING QUALITY BY DESIGN AND THERAPY OUTCOME OPTIMISATION IN PARENTERAL DRUG DEVELOPMENT

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Introduction: Parenteral drug delivery remains a cornerstone of modern therapeutics, particularly with the increasing prevalence of biologics and advanced therapy medicinal products. Traditionally, development efforts have focused on ensuring product quality through sterile manufacturing, stability, and physicochemical characterisation. However, evolving healthcare systems and patient expectations have shifted attention toward patient-centricity, highlighting that therapeutic success depends not only on product quality but also on administration conditions, usability, and patient adherence. Consequently, there is a growing need to expand pharmaceutical development frameworks beyond product-focused quality to ensure consistent and meaningful therapeutic outcomes.

Objectives: This work aims to explore how Quality by Design (QbD) principles can be extended beyond manufacturing to support the optimisation of therapy outcomes. The objective is to identify critical factors influencing not only regulatory compliance and product quality but also real-world clinical performance and patient adherence.

Materials and Methods: A structured literature-based analysis was conducted using recent scientific publications, regulatory guidelines, and industry reports, with emphasis on recent regulatory perspectives and patient-focused development approaches. QbD principles and risk-based approaches were applied to map the transition from traditional Critical Quality Attributes (CQAs) to Critical-to-Quality (CTQ) factors, defined as elements essential for ensuring reliable and clinically meaningful therapeutic outcomes. The framework integrates manufacturing considerations with patient-focused development and real-world performance aspects.

Results and Discussion: The analysis indicates a paradigm shift in parenteral drug development, in which "quality" is increasingly defined by therapeutic performance under practical word conditions. In addition to classical CQAs, outcome-relevant CTQ factors include route of administration, device usability, dosing frequency, stability under real-world conditions, and patient adherence. The expansion of home-based care and self-administration further emphasises the importance of usability and patient experience in ensuring therapeutic success.

Integrating QbD with outcome-oriented design enables alignment between regulatory compliance and flexible development strategies that account for diverse administration environments. Extending risk assessment frameworks to include patient-related variables supports the development of more robust and resilient therapies and may reduce the burden on healthcare systems. However, a key challenge remains the definition and measurement of outcome-related quality attributes, particularly in real-world settings, where variability in patient behaviour and administration practices can significantly influence therapeutic performance. This highlights the need for integrated frameworks that link pharmaceutical development with real-world data and continuous learning systems.

Conclusion: Extending QbD principles toward therapy outcome optimisation represents a critical evolution in parenteral drug development. By systematically linking pharmaceutical quality with clinical performance and patient-centric considerations, this approach supports the design of thera-

pies that deliver consistent, meaningful outcomes. This integrated framework aligns with emerging regulatory expectations and enhances the overall value of parenteral treatments.

CONTINUOUS-FLOW CUAAC CLICK CHEMISTRY FOR THE SYNTHESIS OF TRIAZOLE-LINKED CYCLODEXTRIN CONJUGATES USING A COPPER GRANULE-PACKED COLUMN

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Introduction: The copper-catalyzed azide–alkyne cycloaddition (CuAAC) is a highly reliable and regioselective click reaction for the synthesis of 1,4-disubstituted 1,2,3-triazoles. Its implementation in continuous-flow systems offers important practical advantages, including enhanced heat and mass transfer, improved safety, simplified catalyst handling, and increased process scalability.

Aims: To develop and evaluate a continuous-flow click-chemistry platform based on a packed-bed column filled with metallic copper granules for the azide–alkyne cycloaddition of 6-monodeoxy-6-monoazido-beta-cyclodextrin and Boc-propargyl-Gly-OH.

Method: The CuAAC reaction was performed under continuous-flow conditions through a fixed-bed reactor packed with copper granules, using 6-monodeoxy-6-monoazido-beta-cyclodextrin as the azide component and Boc-propargyl-Gly-OH as the terminal alkyne partner. The heterogeneous copper bed served as the catalytic medium, enabling continuous substrate conversion and triazole bond formation within the reactor column. The reaction was conducted at elevated temperature and under pressure to support efficient flow operation and to promote catalytic turnover within the packed-bed system.

Results: The packed-bed flow configuration enabled efficient azide–alkyne coupling and afforded the corresponding triazole-linked product with the expected CuAAC regioselectivity. The use of metallic copper granules provided a simple heterogeneous catalytic platform, reducing reliance on soluble copper reagents and facilitating product isolation. The flow format also supported operational robustness and offered a convenient basis for further optimization and scale-up.

Conclusion: Continuous-flow CuAAC using a copper granule-packed column represents a practical and scalable approach for the synthesis of triazole-linked cyclodextrin conjugates. This strategy combines the intrinsic selectivity of click chemistry with the process advantages of flow chemistry, making it a promising platform for the preparation of functionalized bioconjugates.

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NEW CARBAMATE PSEUDO-IRREVERSIBLE BUTYRYLCHOLINE ESTERASE INHIBITORS

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Alzheimer's disease (AD) is a complex, progressive neurodegenerative disorder characterized by pathological alterations in the central nervous system, including cholinergic dysfunction, accumulation of amyloid-β plaques and oligomers, hyperphosphorylation of tau protein, and neuroinflammation. Butyrylcholinesterase (BChE) has emerged as an important target in the development of novel therapeutic agents for AD, as it contributes to cognitive decline by modulating cholinergic neurotransmission.

In this study, five novel covalent inhibitors of BChE were designed, synthesized, and biologically evaluated based on the lead compound DP-802. In this scaffold, the urea functional group was replaced with a carbamate moiety to enable covalent interaction with the catalytic residue Ser198 of BChE. Furthermore, the acetamide substituent on the benzene ring was replaced with a nitrile group, which improved the solubility of synthetic intermediates in the organic solvents used during the synthesis, without adversely affecting the aqueous solubility of the final compounds. A series of substituents was introduced on the carbamate moiety to assess their influence on covalent binding to the target enzyme. In addition, ligand design aimed to enhance selectivity toward BChE over acetylcholinesterase (AChE).

The five target compounds were successfully synthesized, isolated, and evaluated in vitro against human acetylcholinesterase (hAChE) and human butyrylcholinesterase (hBChE) using Ellman's assay. Among the tested compounds, the derivative bearing a benzyl substituent exhibited

the highest inhibitory potency toward BChE, showing approximately two orders of magnitude greater activity compared to the analogue containing a directly attached phenyl group on the nitrogen atom. However, the compounds did not demonstrate strong selectivity for hBChE, as the most active derivatives showed only approximately 10-fold selectivity over hAChE, whereas a selectivity margin of at least three orders of magnitude would be desirable. Nevertheless, the most active compounds exhibited pseudo-irreversible inhibition of the target enzyme.

Ferjančič Benetik S, Meden A, Knez D, et al. Transforming ureas into carbamates : from allosteric p38α MAPK ligands to dual BChE/p38α MAPK inhibitors. Bioorganic chemistry. 2025, 165, 1-27.

A DISPROPORTIONALITY ANALYSIS OF ANTI-SEIZURE MEDICATIONS FOCUSING ON SKIN-RELATED ADVERSE DRUG REACTIONS USING THE EUDRAVIGILANCE DATABASE

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Introduction: Anti-seizure medications (ASMs) are frequently associated with cutaneous adverse drug reactions (ADRs), from mild eruptions to severe, life-threatening conditions like Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These skin ADRs often necessitate treatment modification or discontinuation, significantly impacting therapeutic outcomes and highlighting their importance in pharmacovigilance. Large-scale databases like EudraVigilance offer a robust platform for systematic safety signal evaluation in real-world populations.

Aims: This study evaluated the association between ASMs and clinically relevant skin-related ADRs using disproportionality analysis, characterising seriousness and clinical outcomes across pharmacological groups.

Methods: A retrospective pharmacovigilance study was conducted utilising data from the EudraVigilance database spanning a 10-year period (January 1, 2015, to December 31, 2024). Individual case safety reports involving ASMs were identified and classified by the ATC system (N03A) and stratified. Adverse events were coded using the MedDRA; skin-related ADRs were identified within the "skin and subcutaneous tissue disorders" SOC. Seriousness and outcome followed EudraVigilance criteria. Disproportionality analysis was performed using reporting odds ratios (RORs) with 95% confidence intervals (95%CIs) to detect potential safety signals.

Results: After removing duplicates, 291,308 ICSRs corresponding to 245,590 individual cases and 1,134,356 Preferred Terms (PTs) from which a subset of 16,432 skin-related PTs corresponding to 12,707 individual cases were extracted for detailed analysis. The top 5 skin PTs include: drug reaction with eosinophilia and systemic symptoms (DRESS) 4,960 (30.19%), SJS 3,490 (21.24%), TEN 1,874 (11.40%), urticaria 1,795 (10.92%) and erythema multiforme 1,061 (6.46%). Significant associations were revealed. ASMs with strong associations: DRESS with carbamazepine (ROR=2.18, 95%CI [2.10, 2.25] p<0.001) and phenytoin (ROR=1.75, 95%CI [1.65, 1.85] p<0.001); SJS with lamotrigine (ROR=1.84, 95%CI [1.76, 1.92] p<0.001) and phenytoin (ROR=1.36, 95%CI [1.24, 1.47] p<0.001); TEN with lamotrigine (ROR=1.32, 95%CI [1.21, 1.42] p<0.001) and valproate (ROR=1.25, 95%CI [1.09, 1.42] p<0.001); urticaria with gabapentin (ROR= 5.25, 95%CI [5.06, 5.44] p<0.001) and pregabalin (ROR=4.03, 95%CI [3.88, 4.19] p<0.001); erythema multiforme with lamotrigine (ROR=1.41, 95%CI [1.28, 1.55] p<0.001) and carbamazepine (ROR=1.28, 95%CI [1.14, 1.42] p<0.001). ASMs with weak associations include: DRESS with topiramate (ROR=0.44, 95%CI [0.03, 0.85] p<0.05) and lacosamide (ROR=0.56, 95%CI [0.24, 0.88] p<0.001); SJS with pregabalin (ROR=0.37, 95%CI [0.13, 0.60] p<0.05) and topiramate (ROR=0.47, 95%CI [0.011, 0.95] p<0.05); TEN with oxcarbazepine (ROR=0.60, 95%CI [0.22, 0.98] p<0.01); urticaria with phenytoin (ROR=0.28, 95%CI [0.02, 0.54] p<0.05) and carbamazepine (ROR=0.33, 95%CI [0.18, 0.49] p<0.001); erythema multiforme with phenytoin (ROR=0.38, 95%CI [0.087, 0.68] p<0.05). Characterizing their seriousness and clinical outcomes, valproate was strongly associated with life-threatening PTs ROR=1.25, 95%CI [1.10, 1.40] p<0.001, lamotrigine with prolonged hospitalization ROR=1.20,

95% CI [1.14, 1.26] p<0.001 and phenytoin with fatal outcomes ROR=1.51, 95%CI [1.26, 1.76] p<0.001.

Conclusion: This large-scale pharmacovigilance study identified significant associations between ASMs and severe skin ADRs like DRESS, SJS, and TEN, with distinct risk profiles. In terms of seriousness and outcome, valproate was linked to life-threatening and phenytoin was linked to fatal outcome. These findings underscore the critical importance of continuous pharmacovigilance monitoring and disproportionality analysis to guide clinical decision-making and enhance patient safety.

DEVELOPMENT AND CHARACTERIZATION OF A NOVEL CALCIUM BUTYRATE-LOADED SPRAYABLE GEL FOR THE TREATMENT OF ATOPIC DERMATITIS

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Atopic dermatitis (eczema) is a chronic dermatological disorder characterized by impaired skin barrier function and severe inflammation. Calcium butyrate (CAB), a salt form of butyric acid, possesses significant potential in maintaining cellular viability through its ability to support epithelial cell growth and modulate inflammatory responses. This study aims to develop and characterize an innovative sprayable gel formulation for use in eczema treatment that utilizes the skin barrier-repairing properties of CAB, can be applied to damaged and sensitive skin tissue without causing mechanical irritation, and increases patient compliance. To optimize the fluidity and tissue adhesion properties of the sprayable gel system using Carboxymethyl Cellulose (CMC), a gelling agent, at three different concentrations (1.0%, 1.5%, and 2.0% w/v). In the developed drug loaded formulations, the CAB concentration as the active pharmaceutical component was kept constant at 1% (w/v). Additionally, 1% (w/v) glycerine was added to all formulations as a moisturizing agent to support stratum corneum hydration. Characterization studies showed that both the gelling polymer concentration and the addition of the active substance had a significant effect on the physicochemical and mechanical properties of the system. pH values of the blank formulations, measured using a digital pH meter, ranged from 6.98 to 7.27, while the pH values of the CAB-loaded formulations averaged 8.07 ± 0.209, and both groups were found to be suitable for topical application. Viscosity measurements performed at room temperature using a Brookfield viscometer showed values ranging from 331 cP (F1-Blank) to 10973 cP (F3-Blank) for the blank gels, while these values increased in the loaded gels due to the tightening of the network structure with the addition of CAB. While formulation F1 maintained the highest fluidity with an average of 534 cP, the viscosity of formulation F3 reached an average of 12013 cP. Texture Profile Analysis (TPA) results supported these findings; firmness values of the blank formulations ranged from 20.1 g (F1-Blank) to 154.1 g (F3-Blank), while mechanical resistance increased with the addition of the active substance. Considering all the se data and sprayability results, formulation F1 loaded with CAB exhibited the most ideal mechanical properties for contactless application to lesioned skin, giving the lowest firmness (~30.4 g) and the largest spray area (~3.69 cm^2). In in vitro release tests, formulation F1 achieved a cumulative CAB release of 98.5% after 6 hours, while this rate remained at 56.6% in formulation F3 due to increased polymeric network density. In light of the findings, the sprayable gel formulation (F1) containing 1% CMC stands out as the most ideal carrier system due to its optimum rheological properties, successful spray pattern, and superior drug delivery capacity. This innovative system has strong dermatological potential in preventing mechanical irritation in eczematous skin, increasing patient compliance, and maximizing the therapeutic efficacy of CAB.

PHYTOCHEMICAL CHARACTERIZATION AND INVESTIGATION OF THE BIOLOGICAL ACTIVITY OF OSAGE ORANGE (*MACLURA POMIFERA* L.)

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Introduction: Plant-derived metabolites continue to be important sources of potential active pharmaceutical ingredients (APIs) today. Following this approach, our work aimed to investigate Osage orange (*Maclura pomifera* (Raf.) C.K.Schneid), which is used as both a horticultural plant species and a raw material in wood industry. We focused on parts of the plant that are currently not made use of and are treated as waste. Aligned with modern environmental sustainability efforts, their utilization in the pharmaceutical industry could become possible.

Aims: The aim of our study was the polyphenol profiling of *Maclura pomifera* and the characterization of the membrane permeability, stability, and antiproliferative properties of its main isolated compounds.

Methods: Extracts were prepared from different plant parts using solvents of varying polarity and analyzed by UHPLC-Orbitrap-MS. Compounds were isolated by flash chromatography and semi-preparative RP-HPLC and identified by HR-MS and NMR. Membrane permeability was assessed using the PAMPA-BBB and PAMPA-GI models. Chemical stability of the isolated compounds was evaluated at physiological pH values (pH 7.4, 6.8, and 1.2). The antiproliferative activity was measured by the Alamar Blue assay.

Results: Four major compounds, the prenylated isoflavones osajin, pomiferin, 6,8-diprenylorobol, and 6,8-diprenylgenistein were isolated. The ability of the Osage orange compounds to cross membranes by passive diffusion was investigated for the first time. Results showed no membrane permeation either in the PAMPA-BBB or in the PAMPA-GI model; compounds were undetectable in the acceptor phase and were present only at low concentrations in the donor phase. Subsequent stability studies indicated that most compounds are unstable at the investigated pH values. All compounds were unstable at pH 7.4, and among acidic conditions (pH 1.2). At pH 6.8, pomiferin and 6,8-diprenylorobol showed significant degradation ($p<0.05$), while osajin and 6,8-diprenylgenistein were stable.

Conclusion: In our work, we provided new data on the chemical and biological characteristics of prenylated isoflavonoids from *M. pomifera*, which may lay the foundation for the further investigation of the plant as the source of drug candidate compounds.

DESIGN AND PHYSICOCHEMICAL CHARACTERIZATION OF CALCIUM BUTYRATE-LOADED MICROEMULSION SYSTEM FOR TOPICAL APPLICATIONS

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UVB exposure accelerates the photoaging process by increasing the production of inflammatory cytokines in the skin. In particular, the increase in IL-6 levels is closely associated with oxidative stress, collagen degradation, loss of elasticity, and the formation of fine wrinkles. In this context, the ability of butyric acid to suppress UVB-induced IL-6 production is considered an important anti-aging mechanism in preventing skin aging. Calcium butyrate (CAB), a salt form of butyric acid, is an important energy source for colonocytes. It also contributes to maintaining cellular viability by supporting the development of epithelial cells. In this study, pseudoternary phase diagrams were created to develop various microemulsion (ME) systems. Isopropyl myristate (IPM) was used as the oil phase, Span 80 and Tween 20 as surfactants, 1,2-propanediol as cosurfactant, and distilled water containing 2.5% P188 as the aqueous phase. In the final stage, the CAB concentration in the microemulsion formulations was adjusted to 1% (w/w).

The pH values of the formulations were measured using a digital pH meter, yielding an average of 6.13 ± 0.07, indicating compatibility with the physiological environment and suitability for topical applications. Meanwhile, the empty microemulsion system showed a lower average pH of 5.40 ± 0.09.

Refractive index values were performed using a Krüss Optronic digital refractometer, obtained from CAB-ME ranged from 1.4494 to 1.4497 (±0.00017), confirming the transparent, isotropic,

and homogeneous nature of the system. Similarly, the empty microemulsion yielded an average refractive index of 1.4503 ± 0.0005. Viscosity measurements were performed at room temperature using a Brookfield viscometer, with an average value of 122.67 ± 1.15 cP. Meanwhile, viscosity values obtained from the empty microemulsion showed average of 198 ± 2 cP.

Particle size analyses were performed with a Malvern Zetasizer, yielding an average value of 13.56 ± 1.26 nm for the CAB-ME system. Similarly, the empty microemulsion system exhibited an average particle size of 13.51 ± 0.89 nm. Polydispersity index (PDI) values were performed with a Malvern Zetasizer, for the CAB-ME formulation averaged 0.209 ± 0.07, indicating a narrow particle size distribution and a homogeneous system. In contrast, the ME formulation exhibited a higher PDI value of 0.349 ± 0.067, reflecting a broader size distribution.

Conductivity values were performed with a Malvern Zetasizer, for the CAB-ME formulation averaged 0.057 ± 0.075 mS/cm, indicating a water-in-oil (W/O) microemulsion structure, whereas the ME system showed a significantly lower conductivity (~0.001 mS/cm), reflecting reduced ionic mobility, and a refractive index of 1.4503 ± 0.0005 mS/cm.

In conclusion, the addition of calcium butyrate to the microemulsion system did not lead to any deterioration in the system's fundamental colloidal properties. On the contrary, the nanometric particle size, low PDI, appropriate pH, and homogeneous structure were preserved. These findings demonstrate that the CAB-ME system is a suitable and stable microemulsion formulation for pharmaceutical and dermatological applications.

PREPARATION AND INVESTIGATION OF ARTEMISIA ANNUA L. LOADED ALGINATE HYDROGELS WITH EXCIPIENTS

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Artemisia annua is a medical plant, that belongs to the Asteraceae family, commonly known as sweet wormwood or Qinghao. The medicinal value of A. annua extends beyond malaria, as it has been explored for its antiviral, antifungal, antimicrobial, anticancer, and anti-inflammatory properties. There is an extensive research data available on the internal use of the herb, however, there are few studies on the topical use of Artemisia annua and its potential excipients.

Hydrogels are three-dimensional, hydrophilic polymer networks that can retain large amounts of water, making them highly useful for biomedical applications such as wound healing, drug delivery, and tissue engineering. Sodium alginate, a naturally derived polysaccharide from brown seaweed, is widely used in the food, pharmaceutical, and biomedical industries for its biocompatibility and non-toxic properties. It is characterized by its ability to form gels in the presence of divalent cations like calcium, which cross-link its polymer chains to create a stable gel structure.

Dexpanthenol (DP), which has skin-protective, moisturizing, and healing properties, was used as an excipient. It is a precursor of pantothenic acid (vitamin B5), which is essential for maintaining healthy skin. Clinical studies have demonstrated that 5% dexpanthenol promotes faster skin regeneration, reduces transepidermal water loss and enhances hydration, making it effective for treating various skin conditions.

Hyaluronic acid (HA) is widely used in topical formulations because of its exceptional ability to retain moisture and providing hydration. HA supports skin healing and repair by maintaining a moist environment that promotes tissue regeneration, making it an important base for wound healing processes.

The aim of the study was to formulate a stable and well-tolerated drug carrier with different excipients and to evaluate the antioxidant and wound-healing effects of these formulations. Hydrogels are potentially good drug carriers for external drug delivery, and the safety of the internal use of sodium alginate has been mentioned in previous articles. In order to characterise the formulations, different dosage form studies were performed, and moisture content, water retention, pH, and gelation time of the hydrogels were measured. The physico-chemical characterization of Artemisia annua was performed using LC-ESI-MS. In vitro biocompatibility and wound-healing potential were evaluated using cytotoxicity and

scratch assays on human keratinocyte (HaCaT) cells, while in vivo wound-healing efficacy was assessed using a rat excision wound model. DPPH, CUPRAC, and FRAP antioxidant assays were performed to investigate the antioxidant effects of the formulations.

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DEVELOPMENT OF THERMORESPONSIVE POLOXAMER-BASED IN SITU GEL FOR NASAL DELIVERY OF METRONIDAZOLE

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Introduction and aim: Nasal in situ gelling systems represent advanced drug delivery platforms that combine the ease of administration of liquid formulations with the prolonged residence time and controlled release of gels formed directly at the site of application. Thermoresponsive systems based on poloxamers are particularly attractive due to their ability to undergo sol–gel transition at physiological temperatures, improving drug retention within the nasal cavity and potentially enhancing local therapeutic efficacy. The incorporation of mucoadhesive polymers such as natural gums may further improve formulation performance by reducing mucociliary clearance. The aim of this study was to develop and comprehensively characterize a thermoresponsive in situ nasal gel containing metronidazole, based on poloxamer 407 (P407), poloxamer 188 (P188), and guar gum (GG), and to evaluate the influence of formulation composition on physicochemical, rheological, spray, and drug release properties.

Materials and methods: Eight formulations were prepared using a 2^3 factorial design, varying concentrations of P407 (14–16%), P188 (0–2%), and GG (0–0.02%). Formulations were produced by the cold dispersion method and evaluated in terms of visual characteristics, pH, apparent viscosity at 20 °C, gelation time at 34 °C, sprayability (dose uniformity and spray pattern), oscillatory rheological properties, gelation mechanism, and in vitro drug release in simulated nasal conditions.

Results: All formulations exhibited acceptable clarity, homogeneity, and pH values (6.74–6.87), suitable for nasal administration. Apparent viscosity ranged from approximately 15 to 41 mPa·s, enabling adequate sprayability. Increasing polymer concentration, particularly P407, significantly increased viscosity and accelerated gelation, while P188 prolonged gelation time or inhibited gel formation in certain systems. Guar gum slightly increased viscosity and reduced gelation time. Sprayability studies demonstrated good dose reproducibility (RSD < 6.2%) and symmetrical spray patterns (circularity > 0.8). A strong negative correlation ($r = -0.73$) was observed between viscosity and spray spread, indicating reduced atomization efficiency with increasing viscosity. Rheological analysis confirmed thermally induced sol–gel transition, with elastic modulus (G′) values ranging from 27.4 to 6697 Pa at 34 °C. Formulations with higher P407 content formed stronger gel networks, while systems containing P188 at lower P407 concentrations failed to gel, exhibiting predominantly viscous behavior. Temperature sweep analysis revealed a characteristic sigmoidal increase in G′, confirming micelle-driven gelation. All formulations exhibited rapid drug release, with complete metronidazole release achieved within 30 minutes. Formulations with higher gel strength showed slower initial release, indicating a relationship between gel structure and diffusion-controlled release kinetics.

Conclusion: The developed thermoresponsive nasal in situ gel systems demonstrated suitable physicochemical, rheological, and spray properties for nasal delivery. Formulation composition strongly influenced gelation behavior and performance. The formulation containing 14% P407 and 0.02% GG provided the most favorable balance between sprayability, gelation, mechanical properties, and drug release, representing a promising candidate for further development of nasal antimicrobial therapy.

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ASSESSMENT OF CONTENT UNIFORMITY USING PROCESS ANALYTICAL TECHNOLOGY: A CASE STUDY IN THE CONTEXT OF THE U.S. PHARMACOPEIA

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The manufacturing and quality assurance of pharmaceutical products are under strict regulation. One important element of this process is the assessment of content uniformity (CU).

The application of Process Analytical Technology (PAT) and Quality by Design (QbD) principles offers new opportunities for improving and controlling manufacturing processes and product quality. Unlike many other application areas, there is currently no clear guidance from the U.S. Pharmacopeia (USP) on the PAT-based evaluation of CU.

This work aims to investigate several statistical approaches for the PAT-based CU assessment. Their compliance with practical and regulatory expectations was also evaluated under USP and Ph. Eur. guidance. Case studies (based on real-life industrial scenarios) were used to investigate the performance of different statistical evaluation approaches.

The simulations confirmed that analytical measurement uncertainty has a significant impact on CU decisions when tier 2 testing is performed. Assuming a batch with 100% label claim, 4.0% tablet-to-tablet variability and 5.0% RSD (relative standard deviation) as analytical uncertainty the batch acceptance probability reduced from 100% to 88.3%, eliminating the 'zone of certain acceptance' compared to the analytical uncertainty-free case. However, increasing the sample size could compensate for the impact of increased analytical uncertainty.

Depending on the required level of safety and the manufacturing scenario, between 280 and 20,000 PAT measurements were sufficient for reliable regulatory decisions, even when prediction errors were up to four times higher than those of conventional analytical methods (~1.0–1.5% in RSD). To achieve the same 100% acceptance probability for target batches (100% label claim) as conventional HPLC tier 2 testing, around 280 PAT measurements were required for a batch with 5.0% tablet-to-tablet variability. Meanwhile, reducing the width of the 'indeterminate decision zone' by 95% required approximately 20,000 measurements. In this case, further improvements in analytical precision were less beneficial for CU decision reliability below an 1.49% RSD analytical uncertainty.

Our results indicate that although using PAT methods allows for complete 100% inspection, it is not necessary to make a decision with sufficiently high probability upon CU. As the simulations showed, once a certain sample size is reached, further sampling yields only marginal improvements in decision reliability. Our proposed simulation method can identify these marginal points, offering a basis for implementing PAT-based CU strategies in both real-time release testing (RTRT) and conventional manufacturing environments.

COMPARATIVE STUDY OF INCORPORATION AND ADSORPTION STRATEGIES FOR SELECTED COMPOUNDS ON ALBUMIN NANOPARTICLES

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Albumin-based nanoparticles are widely investigated as carrier systems due to their biocompatibility and versatile binding properties. However, the interaction between the carrier and the active compound may strongly depend on the applied loading strategy, and the comparative evaluation of different approaches under controlled conditions remains limited.

This study aimed to compare incorporation during nanoparticle formation and post-formation adsorption using selected model compounds with differing physicochemical properties. Model compounds were selected to represent distinct physicochemical profiles and interaction mechanisms, including lipophilic terpenes (geraniol and menthol, dominated by hydrophobic interactions) and the ionizable antibiotic sulfamethazine, allowing systematic comparison of hydrophobic versus pH-dependent electrostatic binding. Albumin nano-

particles were prepared by desolvation. Two loading strategies were applied: incorporation during nanoparticle formation and post-formation adsorption onto preformed nanoparticles, with possible subsequent diffusion into the particle matrix. Lipophilic compounds were incorporated during particle formation, whereas adsorption of sulfamethazine onto preformed nanoparticles was evaluated under controlled pH conditions.

Nanoparticles were characterized in terms of size and colloidal stability ranging from 50-300 nm and 7-14 days with a PDI ranging from 0.1 – 0.4 respectively, while loading and adsorption behaviour were evaluated comparatively. The results indicate that incorporation during particle formation favours the association of lipophilic compounds, with dependence on their physicochemical properties. In contrast, adsorption of sulfamethazine was strongly influenced by environmental conditions, particularly pH, reflecting the role of electrostatic interactions and pH-dependent protonation. These findings demonstrate that incorporation is more suitable for hydrophobic compounds, whereas adsorption provides a tuneable approach for ionizable molecules under controlled environmental conditions.

DEVELOPMENT OF INNOVATIVE BUCCAL FILMS FOR THE TREATMENT OF DIFFERENT ORAL DISEASES

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Recently, the use of nystatin- and benzo caine-containing magistral preparations in the treatment of different oral diseases has come to the fore in public pharmacies. Nystatin is a polyene-type antifungal agent that acts by binding to ergosterol, thereby forming a pore on the membrane of the fungal cell and causing its destruction. Benzocaine is a local anesthetic that exerts a local analgesic effect by blocking the influx of sodium ions through sodium channels in excited membranes and the transmission of nerve impulses. Both molecules has poor water solubility and bioavailability, which can be improved by the widely used excipients, cyclodextrins. Buccal patches are a group of innovative pharmaceutical forms, thin polymeric films, which are convenient to use and the release of the active substance is rapid. They increase patient compliance and treatment success.
The aim of our research was to increase the solubility and bioavailability of nystatin and benzocaine with hydroxypropyl-beta-cyclodextrin (HPBCD), to characterize the physicochemical properties of the inclusion complexes, to formulate buccal films and to study their properties. The ratios of the inclusion complexes with the appropriate composition were determined by phase solubility testing. The formulated complexes were characterized by their size distribution and zeta potential, and their morphology was investigated by scanning electron microscopy (SEM). The buccal patches were prepared by solvent evaporation method and the formulated films were characterized by their physical and mechanical properties and thermoanalytical measurements were carried out.

In conclusion, we have successfully increased the water solubility of nystatin and also benzocaine using cyclodextrin. The hydrodynamic diameter of the complexes were in nano-scale and monodisperse distribution and based on the zeta potential results the formulated complexes were stable. In addition to this, we successfully formulated polymer-based buccal patches. Incorporation of the complexes into the buccal patches does not affect their mass and thickness, however, the tensile strength of the drug-containing films increases significantly, yet their elasticity decreases. Based on the thermoanalytical studies the formulated buccal films were thermostable systems.

BIOLOGICAL EFFECTS OF NOVEL CANNABIGEROL DERIVATIVE PFD 45/I ON RENAL CELL CARCINOMA CELLS

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Renal cell carcinoma (RCC) is one of the most common malignancies of the urinary system, accounting for approximately 90% of all kidney cancers, and its global incidence has steadily in-

creased over recent decades. RCC is frequently diagnosed at advanced or metastatic stages due to the lack of specific early symptoms, which significantly limits therapeutic success. Therefore, the identification of novel compounds with improved selectivity and antitumor efficacy is of considerable importance. Cannabigerol (CBG), a non-psychoactive phytocannabinoid derived from *Cannabis sativa*, has demonstrated promising anticancer properties in several tumor types; however, its clinical applicability is restricted by poor aqueous solubility and limited bioavailability. Recent studies on fluorinated cannabidiol and cannabigerol derivatives demonstrated improved biological activity and pharmacological potential. Eight novel CBG derivatives were synthesized and evaluated on human RCC cell lines (CAKI-2 and A498). Cell viability and proliferation were assessed using the Cell Titer-Blue assay, while long-term antiproliferative capacity was further investigated by clonogenic assay. Among the tested compounds, three derivatives exhibited significant antiproliferative activity, with PFD45/I proving to be the most potent at 30 μM. Importantly, clonogenic assay results further confirmed the inhibitory effect of PFD45/I on RCC cell survival and colony-forming ability, supporting its sustained antitumor activity. Notably, PFD45/I demonstrated low cytotoxicity in non-malignant NIH-3T3 fibroblast cells. Preliminary molecular investigations suggest that the compound may influence apoptosis- and proliferation-related signaling pathways. Western blot analysis indicated the possible involvement of the PI3K/Akt/mTOR pathway through modulation of PI3K, Akt, and phosphorylated Akt (p-Akt) expression. Previous studies have also highlighted the importance of cannabinoid-associated signaling in RCC progression and growth inhibition. However, further studies are required to determine whether the observed antitumor effects are mediated primarily through CB1 or CB2 receptors, or a combination of both cannabinoid receptor pathways. Additional investigations are necessary to further characterize its biological properties, clarify precise molecular mechanism of action, and evaluate therapeutic potential in more advanced preclinical models.

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PROCESS SCALE-UP AND TABLETING PERFORMANCE OF HIGH-MASS FIROCOXIB EQUINE CHEWABLE TABLETS

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Manufacturing high-mass chewable tablets containing firocoxib for equine veterinary application presents significant formulation and engineering challenges, particularly in balancing mechanical strength, matrix porosity, and chewability. This study evaluated the systematic process scale-up and technology transfer of a large-mass firocoxib chewable tablet formulation from a single-punch compaction simulator (Medelpharm STYL'One Evolution) to an industrial-scale rotary tablet press (Fette 1200).

Initial small-scale characterization was performed on the compaction simulator to establish the compression profile of the direct-compressed tablet blend. Compaction dynamics, plastic deformation behavior, dwell time dependence, and elastic recovery were systematically analyzed. Using integrated simulation software, the displacement profiles and compression kinematics of the production-scale rotary press were accurately modeled across various production speeds. The transfer strategy focused on mitigating tableting defects common to high-mass matrices, such as capping and lamination caused by air entrapment during high-speed compaction.

Subsequent scale-up runs on the industrial rotary press validated the predictive accuracy of the simulator. Applying a tailored pre-compression profile successfully de-aerated the large powder volume prior to main compaction, ensuring structural integrity without compromising matrix porosity or chewability parameters. Critical quality attributes—including tablet breaking force, friability, weight uniformity, and ejection force—remained consistent during the transition from single-dosing simulation to continuous production.

In conclusion, utilizing a compaction simulator for predictive scale-up significantly reduced the raw material consumption and pilot-scale press downtime. The established compression parameters allowed for a seamless technology transfer,

producing high-mass equine firocoxib chewable tablets with robust mechanical integrity, minimal friability, and suitable properties for veterinary administration.

DEVELOPMENT AND VALIDATION OF A SIMPLE HPLC METHOD FOR THE DETERMINATION OF KETOROLAC TROMETHAMINE

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Introduction: Ketorolac tromethamine (KT) is a non-steroidal anti-inflammatory drug with proven efficacy, especially in the treatment of ocular pain and inflammation (1). The aim of this study is to develop and validate a High-Performance Liquid Chromatography (HPLC) method compliant with international standards for the determination of KT levels in preclinical and clinical studies.

Materials and MethodsA MetaSil AQ reversed-phase column is used in chromatographic separation. An isocratic mixture containing methanol: water:glacial acetic acid (70:29:1, v/v/v) was used as the mobile phase.

For method calibration, a 1000 μg/mL KT stock solution was prepared, and standard solutions at concentrations of 1, 2.5, 5, 10, 25, and 50 μg/mL were prepared by dilution. To assess the reliability of the analytical method, linearity, precision, accuracy, limit of detection (LOD), limit of quantitation (LOQ), and stability were evaluated.

Results and Discussion: The developed HPLC method showed that results in the 1-50 μg/mL concentration range were proportional to analyte concentration and exhibited excellent linearity. The linear regression equation for the calibration curve was y = 68.471x – 7.8483, and the R2 value was 0.9999. In studies conducted to test the sensitivity of the method, the signal-to-noise ratio at 1 μg/mL concentration was measured as 54,3. With these obtained data, the LOD was calculated as 0.055 μg/mL and the LOQ as 0.184 μg/mL. To verify the repeatability of the method, consecutive measurements were performed over three days, and the resulting coefficient of variation (%CV) remained below 2%, indicating high precision. In the accuracy and recovery analyses, rates ranged from 97.35% to 106.07%. Additionally, during the 48-hour analysis of the 10 μg/mL KT solution, no degradation peak was observed, showing that the drug remained completely stable.

Conclusion: In this study, a sensitive, accurate, and reproducible HPLC method compliant with ICH guidelines was successfully validated for the quantitative determination of KT. This developed sensitive analytical method can be safely used to examine the in vitro release profiles of innovative drug delivery systems, as well as KT in bulk and pharmaceutical dosage forms. Thereby, it may contribute to preclinical and clinical studies.

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CLINICAL DECISION SUPPORT SOFTWARE UNDER MDR: REGULATORY CHALLENGES AND A PRACTICAL EVALUATION FRAMEWORK FOR CLINICAL USE

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Background: Clinical decision support software (CDSS) is playing an increasingly prominent role in pharmacy practice, particularly in dose optimization and the prevention of medication errors. Aims: However, there is currently no standardized, operational framework for evaluating CDSS that simultaneously reflects regulatory, clinical, and usability dimensions. The regulatory environment may delay market access, hinder innovation, and lead to the withdrawal of certain solutions. The complexity of the regulatory landscape poses challenges during development and clinical implementation. For users, the reliability and clinical validation background of CDSS solutions are often unclear, while information overload and alert fatigue may reduce effectiveness and contribute to clinically relevant alert overrides and missed critical alerts. The lack of standardized evaluation criteria limits comparison of different CDSS solutions, contributing to lower user acceptance and suboptimal utilization. From the patient

perspective, digital health applications vary substantially in validation, regulatory oversight, and clinical integration; although they can support self-monitoring and therapeutic adherence, inadequate validation and/or integration may also pose risks. Consequently, neither patients nor healthcare professionals currently have access to an unified, structured framework to assess the quality and clinical utility of digital health solutions.

Methods: The introduction of EU MDR 2017/745 has created significant challenges in the development and application of software-based medical devices. While the MDR software classification system is conceptually aligned with the IMDRF Software as a Medical Device (SaMD) framework, in practice places greater emphasis on the clinical significance of decisions and the severity of potential harm, resulting in a more conservative classification approach. Consequently, Rule 11 has shifted a substantial proportion of CDSS into higher risk classes, reducing the proportion of low-risk (Class I) solutions and increasing notified body involvement. This represents a barrier for smaller developers and, may negatively impact innovation.

Under the current regulatory framework, developers must precisely define the intended purpose and the extent of decision support at the design stage, as these directly determine risk classification. For clinical pharmacists, it is expected that CDSS systems provide patient-specific, guideline-based, and clinically relevant recommendations, while minimizing alert fatigue, which may compromise both usability and patient safety.

Results and discussion: Although the primary objective of the MDR was to strengthen patient safety, its impact on the balance between patient safety and innovation remains unclear. Regulatory shortcomings may affect market availability and may hinder innovation. Within the ongoing revision process, the modification of Rule 11 toward a more differentiated, risk-based approach has been proposed.

Conclusions: In response to these challenges, this work proposes a practice-oriented, semi-quantitative, scoring-based evaluation system for the structured, reproducible, and auditable assessment of CDSS. The model is based on a multidimensional set of criteria encompassing regulatory compliance, clinical validation, patient safety, transparency, and workflow integration. Scoring across these domains results in a composite value that enables quantitative comparison of different systems and supports more objective assessment of their clinical utility, including use in procurement and implementation decisions. The proposed approach aims to bridge the gap between regulatory requirements and real-world clinical usability by transforming complex regulatory and clinical considerations into a unified, operational evaluation tool.

APPLICATION OF ARTIFICIAL INTELLIGENCE IN PHARMACEUTICAL TECHNOLOGY: PREDICTION, MODELING, AND OPTIMIZATION OF TABLET DISSOLUTION PROFILES

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Introduction: Traditional optimization of tablet formulations and the experimental determination of drug release profiles are highly time-consuming and resource-intensive processes. Due to the vast number of potential formulation variations within a factorial space, physical testing of every possible combination is practically impossible. Recently, Artificial Neural Networks (ANNs) have emerged as robust machine learning tools capable of learning complex, non-linear relationships between formulation parameters and critical quality attributes such as dissolution rate, often surpassing traditional linear empirical models. Integrating ANNs into pharmaceutical development provides a pathway to minimize trial-and-error experimentation and accurately predict release kinetics in silico.

Objective: The primary objective of this research is to develop and validate an Artificial Intelligence (AI) model capable of predicting the in vitro drug release profiles of tablets based solely on their quantitative excipient composition and physical parameters.

Methods: Using a factorial experimental design, we mapped out 36 distinct formulations for 500 mg theophylline tablets (with a constant 50 mg Active Pharmaceutical Ingredient (API) content). The variable factors include the amounts of croscarmellose sodium (superdisintegrant), hydroxypropyl methylcellulose (hydrophilic matrix), ethylcellulose (hydrophobic matrix), filler composition (microcrystalline cellulose and lactose), as

well as the tablet diameter (8 vs. 10 mm). Following powder compression, dissolution testing will be performed in simulated gastric fluid according to pharmacopoeial standards. The resulting 36 distinct profiles will serve as our core dataset. We will train the AI model using an 80/20 split: 80% of the data will train the model the underlying formulation-release relationships, while the remaining 20% will be set aside as an independent test set for prediction.

Results: The formulation design space has been successfully established. Physical laboratory measurements are currently underway. Based on the selected variables, we expect significant variations in release kinetics dictated by the hydrophilic and hydrophobic polymer ratios. We anticipate that the trained AI model will reliably predict the dissolution profiles of the test set with high accuracy by recognizing the hidden patterns in the training data.

Conclusions: Integrating AI into pharmaceutical technology has the potential to replace extensive trial-and-error laboratory work. By significantly reducing the number of required experiments, this predictive approach will make future formulation and optimization much faster and more cost-effective.

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ENHANCING SOLUBILITY AND BIOAVAILABILITY OF POORLY WATER-SOLUBLE DRUGS IN VETERINARY MEDICINE

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Poor aqueous solubility remains one of the most critical barriers to achieving adequate bioavailability for many active pharmaceutical ingredients (APIs), particularly in veterinary medicine, where interspecies physiological variability further complicates drug delivery. Enhancing solubility and dissolution behavior is therefore essential not only for therapeutic efficacy but also for dose optimization and improved treatment compliance in animals.

Amorphous solid dispersions (ASDs) represent a widely applied and effective strategy to address solubility limitations. In this work, ASDs were prepared using hot-melt extrusion (HME), a solvent-free, scalable, and continuous manufacturing technology. HME enables the molecular-level dispersion of APIs within polymer matrices, resulting in reduced crystallinity, enhanced wettability, and improved dissolution performance.

In veterinary formulations, however, successful drug delivery requires more than physicochemical optimization. Especially for pets, palatability is a key determinant of voluntary intake, making the incorporation of flavoring agents and other excipients indispensable. These components, while improving acceptability, can significantly influence drug release, solubility, and absorption. Their impact must therefore be carefully evaluated during formulation development.

To better understand and predict *in vivo* performance, increasing emphasis is placed on the development of biorelevant *in vitro* methods capable of simultaneously assessing dissolution and absorption processes. These dissolution–permeation models aim to mimic the gastrointestinal conditions of target animal species, including pH variability, composition of intestinal fluids, and membrane permeability. Such systems can provide valuable insight into the interplay between formulation composition and drug bioavailability.

Importantly, these *in vitro* approaches play a key role in reducing the reliance on animal experiments during the development phase. By enabling early-stage prediction of *in vivo* behavior, they support more informed decision-making regarding the final formulation, while significantly lowering development costs and ethical burden. The selection of the optimal formulation can thus be increasingly supported by *in vitro* dissolution–permeation measurements, minimizing the need for extensive *in vivo* testing. Nevertheless, the development of robust and predictive biorelevant models remains challenging. Species-specific gastrointestinal differences, the limited availability of standardized test conditions, and the complexity of integrating biorelevant dissolution and permeation into a simple, reproducible and cost-effective experimental framework all pose significant obstacles.

Integrated approach not only enhances bioavailability and palatability but also contributes to more efficient, cost-effective, and ethically responsible pharmaceutical development in veterinary medicine.

COMPARATIVE EVALUATION OF DIFFERENT ADDITIVE MANUFACTURING PROCESSES FOR 3D-PRINTED TABLETS

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Additive manufacturing technologies enable patient-centric medication in the fields of medicine and pharmaceutics. 3D printing is versatile, entire treatment strategies can be built around this technology. In addition to creating personalized medical devices such as braces, casts and implants, tailored solid dosage forms can be created to satisfy the patient's needs and preferences. This can increase patient adherence and compliance, resulting in a higher success rate of the therapy.

There are multiple types of 3D printing technologies, but the most common and widely available are the Fused Deposition Modelling (FDM) and Stereolithography (SLA). This study compares these two additive manufacturing processes using a Creality Ender 3 (Creality 3D Technology Co., Shenzhen, China) and a Prusa SL1S printer (Prusa Research a.s., Prague, Czech Republic) and lists the advantages and disadvantages of each method. The 3D-printable files were generated using the same slicer software but different engines, due to the different principles of the two printing technologies. The design of the tablets represents the dimensions of a standard compressed tablet; including the diameter (10mm), the hight (5mm) and the edge of the tablet (3mm).

The operational background of the different printing methods was introduced and compared. Advanced image-analysis with a digital microscope (Keyence VHX 970, Keyence, Belgium) was executed to evaluate and compare the quality of the final products, allowing conclusions to be drawn about which method is the most suitable for a given pharmaceutical and therapeutical task.

As a result, it can be concluded that SLA printing has several advantages over FDM printing, including the minimum two times higher resolution, allowing the more precise formulation of complex structures. Furthermore, the printing time of identically oriented tablets, in case of resin-based printers is largely independent of the object number on the printing plate. In the case of FDM, at 0.1 mm layer height, the slicer estimation was 5239 seconds, whereas the SLA printing simulation took 1570 seconds. The average weight of the resin-based tablet was 362.44 mg (n=10) and the FDM printed average was 368.71 mg (n=10).

The main disadvantage is that post-processing and material handling require precision and appropriate safety precautions. The process evaluation of the additive manufacturing technologies is inevitable for the further application of them in personalized therapies.

MOLECULAR CHARACTERIZATION OF FLUORESCENTLY LABELLED CYCLODEXTRIN DERIVATIVES COMPLEXED WITH ADAMANTANE CARBOXYLIC ACID AND THEIR EVALUATION IN HCT 116 COLORECTAL CARCINOMA CELLS

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Cyclodextrins are cyclic oligosaccharide molecules composed of D-glucopyranose units linked by α-1,4 glycosidic bonds. The three most common types are α-, β-, and γ-cyclodextrins, consisting of 6, 7, and 8 glucose units, respectively. Their characteristic structural feature is a hydrophilic outer surface and a hydrophobic inner cavity, which makes them ideal carriers for poorly soluble, hydrophobic molecules (BCS Class II and IV) and active pharmaceutical ingredients. Owing to their biocompatibility, low toxicity, and versatile host-guest chemistry, cyclodextrins have become widely used tools in drug delivery research.

In biological studies, fluorescently labelled cyclodextrin derivatives (FluoCDs) are frequently used to monitor cellular uptake, intracellular trafficking, and accumulation. However, the interpretation of fluorescence-based measurements requires a detailed understanding of the physicochemical behaviour of these derivatives. Cyclodextrins can form large aggregates through self-association, and they may also undergo

self-inclusion, in which the fluorescent moiety becomes embedded within the cyclodextrin cavity, resulting in an artificially enhanced fluorescence signal. To prevent self-inclusion, we used adamantane carboxylic acid (AC), which binds to the β-cyclodextrin cavity with high affinity, thereby displacing previously bound molecules.

Our aim was to characterize the complexes formed between fluorescein- and rhodamine-labelled cyclodextrin derivatives and AC, and to compare their behaviour with the corresponding non-labelled cyclodextrins. To achieve this, we performed several physicochemical analyses, including fluorescence intensity measurements, dynamic light scattering (DLS), and UV-VIS absorbance spectroscopy. Additionally, flow cytometry and fluorescence microscopy were conducted on HCT 116 colorectal carcinoma cells to evaluate cellular uptake and intracellular detectability of the FluoCD-AC complexes relative to the native FluoCDs.

The fluorescence and absorbance values of the FluoCD-AC complex were clearly reduced compared to those of FluoCD alone. To determine whether this decrease was caused by the acidifying effect of AC, we also examined the pH-dependence of the process and confirmed that the observed changes were not attributable to pH alterations. DLS measurements revealed a rearrangement in macromolecular size distribution, further supporting the formation of the FluoCD-AC complex.

Flow cytometry demonstrated that the complex is taken up by HCT 116 cells, and fluorescence microscopy confirmed similar internalization patterns to those observed for FluoCD. However, the complex exhibited lower intracellular fluorescence intensity than expected, consistent with the reduced fluorescence observed in solution.

In summary, our results contribute to the correct application and interpretation of FluoCD derivatives in biological studies and emphasize the need for physicochemical characterization to avoid misleading conclusions in fluorescence-based experiments.

CHITOSAN COATED LIPOSOME FOR ORAL DELIVERY OF NADOLOL

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Nadolol (NDL) is a non-selective beta-blocker classified as a BCS Class III drug, exhibiting high aqueous solubility but poor intestinal permeability, which limits its oral bioavailability to approximately 35%. Conventional oral formulations fail to overcome the physiological barriers of the gastrointestinal tract, including acidic pH, enzymatic degradation, and limited mucosal interaction. To address these challenges, this study aimed to develop chitosan-coated liposomal formulations of NDL to enhance gastrointestinal stability, prolong mucosal residence time through mucoadhesion, and ultimately improve oral bioavailability.

Liposomes were prepared via the ethanol injection method using soy phosphatidylcholine (SPC), dicetyl phosphate (DCP), and cholesterol, with or without cinnamon oil, yielding two base formulations (L1 and L2). Chitosan coating was applied by adding low molecular weight chitosan dissolved in 1% acetic acid at varying chitosan-to-lipid ratios (0.1–0.4 w/w). The optimal coating concentration was identified as 0.25 w/w based on particle size, PDI, and zeta potential evaluations. Physicochemical characterization was performed using dynamic light scattering, and encapsulation efficiency along with drug loading capacity were determined by HPLC. Enzymatic degradation studies were conducted in pepsin- and pancreatin-containing media to assess gastrointestinal stability. In vitro drug release was evaluated at pH 1.2 and 6.8 using the dialysis bag method. Cytotoxicity and permeability studies were performed using Caco-2 cell monolayers via the MTT assay and bidirectional transport experiments. Long-term stability was assessed over 12 months under refrigerator, room temperature, and accelerated conditions. Chitosan coating shifted the zeta potential of liposomes from strongly negative (−42.09 to −50.91 mV) to markedly positive (+37.84 to +40.77 mV), confirming successful surface modification. The optimized L1C-NDL and L2C-NDL formulations exhibited particle sizes of 160.10±3.17 nm and 161.00±2.30 nm, with PDI values of 0.19±0.01 and 0.18±0.02, respectively. Encapsulation efficiencies were 56.01±3.70% and 43.87±1.24%, while drug loading capacities

reached 61.47±2.03% and 67.80±0.74%. Enzymatic degradation studies demonstrated that chitosan coating significantly improved liposomal stability in gastric media compared to uncoated formulations. In vitro release profiles revealed controlled and slower drug release at gastric pH (approximately 82–80% at 4 hours), while near-complete release was achieved in intestinal media within 24 hours, consistent with the pH-dependent behavior of chitosan. Cell viability exceeded 95% for both formulations throughout the 72-hour observation period, confirming biocompatibility. Permeability studies showed enhanced apical-to-basolateral transport for chitosan-coated formulations, with TEER value changes remaining well below the 40% threshold, indicating intact monolayer integrity. Stability data over 12 months confirmed that L2C-NDL maintained superior colloidal stability, with minimal fluctuations in particle size, PDI, and zeta potential. Chitosan-coated liposomes represent a promising mucoadhesive oral delivery platform for NDL, offering improved gastrointestinal stability, controlled drug release, and enhanced intestinal permeability. These findings provide a solid preclinical foundation for further in vivo pharmacokinetic evaluation of chitosan-liposome systems as bioavailability-enhancing strategies for BCS Class III antihypertensive agents.

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LIMITATIONS IN PHARMACEUTICAL APPLICATIONS OF POORLY SOLUBLE ANTIOXIDANTS – PREDICTING THE IMPACT OF DIETARY FIBRE AND FOOD MATRIX ON ORAL BIOACCESSIBILITY OF RESVERATROL

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There is a strong scientific rationale for pharmaceutical applications of resveratrol (RES), known for its antiangiogenic, immunomodulatory, antimicrobial, and neuroprotective properties. For these characteristics RES is considered an excellent candidate as bioactive in dietary supplements and functional foods. The major limitation of wider pharmaceutical application of RES is its low and variable oral bioavailability which can be additionally modified due to complex interactions of RES with food matrix (FM), particularly dietary fiber (DF). These interactions haven't been investigated so far and the existing knowledge gap limits the development of specific therapeutic guidelines for RES as the well as formulation of functional foods and enteral formulas containing resveratrol.

The aim of our research was to apply a static in vitro digestion simulation protocol (Infogest®) to investigate the oral bioaccessibility of RES with or without the presence of FM. Additionally, we investigated interactions of different types of DF and resveratrol under gastrointestinal conditions and analyzed the possibility of utilization of obtained data for the prediction of the impact of DF mixtures on RES bioaccessibility.

Ten types of DF were investigated (inulin, oligofructose, dextrin, cellulose (2 chain lengths), citrus fibre (2 chain lengths), gummi arrabicum, apple fibre and pea fibre), and 4 types of DF mixtures. Children's milk formula was used as the model FM (9,9% proteins, 29,6 % fat and 60,5 % carbohydrates- expressed on dry weight). DF characterization included determination of insoluble-, soluble- and total DF, measurement of water- and oil holding capacity and laser diffraction particle size analysis. The content of total and bioavailable RES was determined by HPLC-DAD. Resveratrol bioaccessibility was 86,3±0,81% and was slightly negatively affected by the FM (78,5±0,91%). The impact of DF varied significantly depending on the type of fibre where DF containing the highest amounts of soluble fraction showed s ignificant positive impact (96,5±1,6%-100,5±2,2%; $p<0.05$). Pea fibre and gummi arrabicum showed significant negative impact (73.8±1,6% and 67,4±2.4%; $p<0,05$) probably due to higher protein content (compared to other DF). RES-DF interactions were useful for the prediction of the impact of DF mixtures on RES bioaccessibility ($R^2=0,8989$; $p=0,0141$).

Obtained findings elucidate DF-RES interactions, demonstrate that soluble DF enhances RES bioaccessibility, and validate a predictive model for DF mixtures, paving the way for optimized functional foods and enteral formulas.

SCREENING VAGINAL LACTOBACILLUS CLINICAL ISOLATES USING FREEZE-DRYING SURVIVAL AS A SELECTION CRITERION FOR PROBIOTIC THERAPY OF VAGINAL INFECTIONS

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The human microbiota is a fundamental determinant of host health, contributing to the maintenance of physiological homeostasis and protection against disease. The vaginal microbiota plays a key role in maintaining urogenital health, and disruption of its normal Lactobacillus-dominated composition is strongly associated with vaginal dysbiosis and infection. Since these infections often recur, restoring a healthy vaginal microbial balance is considered an important therapeutic objective (1,2). In this context, administration of selected vaginal Lactobacillus strains as probiotics represents a promising strategy for both the treatment and prevention of vaginal infections. However, the development of solid probiotic dosage forms requires bacterial strains that can withstand dehydration processes while retaining sufficient viability. The aim of this study was to perform a preliminary screening of vaginal Lactobacillus clinical isolates for their suitability for formulation development, using freeze-drying survival as a key selection criterion.

Twenty candidate strains isolated from healthy vaginal microbiota were cultivated under identical, non-optimized conditions to enable standardized comparison. Briefly, bacterial cultures were grown in MRS medium under anaerobic conditions, washed twice with cold 4% sucrose, resuspended in ultrapure water, and further diluted either with water or with 4% trehalose solution. The resulting suspensions were frozen at -80 °C and freeze-dried. Viability before freeze-drying and immediately after reconstitution of lyophilizates was determined by the drop plate method and expressed as colony-forming units (CFU). Samples were analysed in duplicate.

The highest pre-drying concentration was achieved by Limosilactobacillus vaginalis LVA4 (12.0 log CFU), while the eleven tested Lactobacillus crispatus strains showed a broad range of concentrations from 6.4 to 11.2 log CFU. L. jensenii and L. gasseri strains reached 8.4–11.3 log CFU/mL and 9.7–11.3 log CFU, respectively. All eleven L. crispatus strains, as well as Limosilactobacillus vaginalis LVA4, retained post-drying viability above the predefined acceptance threshold of 5.87 log CFU in at least one tested condition. In contrast, L. jensenii and L. gasseri strains were noticeably more sensitive, since only L. jensenii LJE47 and LJE48 remained above the threshold, whereas the other L. jensenii strains and both L. gasseri strains yielded no detectable viable cells irrespective of trehalose addition. Notably, L. crispatus LCR14 and LCR25 showed less than 0.5-log viability loss during freeze-drying, indicating particularly high robustness. Trehalose did not provide a consistent protective effect across strains.

Overall, this screening identified L. crispatus LCR14, L. crispatus LCR25, and Limosilactobacillus vaginalis LVA4 as the most promising candidates for further development of solid vaginal probiotic dosage forms intended for the treatment and prevention of vaginal infections.

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METRONIDAZOLE-LOADED BUCCAL FILMS AS A POTENTIAL PLATFORM FOR PERIODONTAL THERAPY: DEVELOPMENT AND CHARACTERIZATION

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Introduction: Periodontal disease represents a

global public health concern, with increasing prevalence among the population aged 30 years and older, associated with reduced quality of life and increased risk of metabolic diseases. Treatment aims to manage inflammation by eliminating bacterial biofilm and promoting tissue regeneration. Antimicrobial-loaded buccal films represent a promising scaffold for local periodontal therapy, owing to their flexibility, adaptability to the oral microenvironment, and good patient tolerability. Thus, this study aimed to develop and characterize Eudragit L100- and Carbopol 940-based films for potential buccal delivery of metronidazole as a model active pharmaceutical ingredient (API).

Materials and Methods: Eight film formulations containing Eudragit L100 (EL100; 1.5–5%), Carbopol 940 (CP; 0.5–1%), propylene glycol (PG; 25–35% of total polymer mass), and 96% ethanol were prepared by solvent casting. Polymer solutions were cast, dried at 30 °C for 24 h, and cut into 1 x 1 cm pieces. Obtained films were evaluated for visual and tactile characteristics, mass, thickness, folding endurance, surface pH, and swelling index. Metronidazole (MZ, 500 μg/film) was loaded into three selected formulations exhibiting the most favorable properties. Drug content and in vitro release profile were determined by UV spectroscopy and phosphate buffer (pH 6.8) was used as a release medium.

Results and Discussion: All films were milky-white, translucent and homogeneous. Formulations containing 1.5% EL100 were softer, stickier and more elastic than films containing 5% EL100. Film mass ranged from 3.51 ± 0.84 to 9.55 ± 1.49 mg, while thickness ranged from 34.10 ± 3.82 to 83.09 ± 4.69 μm, both parameters expectedly increasing with higher polymer concentration. Folding endurance was evaluated as a measure of film integrity and flexibility and expressed as the number of folds until film breakage. The values ranged from 8.30 ± 0.58 for formulations containing 0.5% CP, 5% EL100 and 25% PG, to >100 for films containing 1% CP and 1.5% EL100. Surface pH was acidic (2.53-2.66), as anticipated, due to the presence of polyacrylic acid (CP). Films containing 0.5% CP and 5% EL100 exhibited the lowest swelling (50% after 2 h), whereas films containing higher concentration of CP and lower concentration of EL100 doubled in mass after 15 minutes, exhibiting superior swelling properties. Formulations 3 (0.5% CP, 1.5% EL100, 35% PG), 5 (1% CP, 1.5% EL100, 25% PG) and 7 (1% CP, 1.5% EL100, 35% PG) were selected for MZ incorporation. MZ loading did not significantly affect film appearance, mass, thickness and pH, due to the low dose of MZ. Folding endurance remained >100 for formulations 5 and 7, and improved in formulation 3. Drug content was approximately 90% in all three films. Although swelling index decreased, it remained above 100% after 2 h. All medicated formulations exhibited almost immediate MZ release, reaching a plateau within 15 minutes.

Conclusion: Preliminary findings suggest that EL100/CP-based buccal films represent a promising platform for buccal antibiotic delivery. Future studies should focus on the comprehensive evaluation of their mechanical and mucoadhesive properties, as well as the optimization required to achieve controlled drug release.

THE IMPACT OF POLYMERIC CARRIER AND RESVERATROL LOADING ON ITS SOLID-STATE CHARACTERISTICS IN MESOPOROUS CARRIER-BASED SOLID DISPERSIONS OBTAINED BY HOT MELT EXTRUSION

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The type of polymeric carrier and drug loading may influence whether a drug remains amorphous and physically stable in solid dispersions during storage. In mesoporous systems, both the type of polymer and amount of drug loaded relative to the pore capacity of mesoporous carrier may influence recrystallization risk (1–3).

The aim of this study was to evaluate the effect of carrier and resveratrol (RSV) loading on storage-related changes in RSV melting enthalpy of hot-melt extruded (HME) solid dispersions. A series of hot-melt extruded solid dispersions was prepared using either single polymers (PEG 6000, Eudragit® EPO, HPMC AS MMP) or their mixtures with PEG 6000 at different proportions, in combination with mesoporous silica carriers. RSV loading was varied between 20 and 40% (w/w). Solid-state behavior was characterized by differential scanning calorimetry immediately after processing and after storage under accelerated conditions for three months.

After processing, a decrease in RSV melting enthalpy was observed in all formulations relative to

crystalline RSV, consistent with formation of a partially amorphous system. Polymer selection across formulations influenced storage-related physical stability, with polymer mixtures with PEG tending toward lower melting enthalpies. The effect of RSV loading on enthalpy changes varied across formulations. Overall, no statistically significant effect of polymer system or RSV loading on storage-related recrystallization was identified, although non-significant trends suggested formulation-dependent behavior.

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