

CONFERENCE ABSTRACTS

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Drug delivery medicine

Integrative dermaceutical solutions: Development of camwood face cream, wash, toner & serum for improved dermatological health

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Background: The convergence of dermatology and pharmaceutical science introduces innovative therapeutic skincare solutions known as dermaceuticals. These products bridge the gap between traditional cosmetics and pharmaceuticals, combining aesthetics with clinical efficacy. To explore this intersection in enhanced pharmaceutical care and service delivery, this study focused on the development of dermaceutical face cream, cleanser, toner and serum using the heartwood of camwood, which are rich in bioactive compounds.

Purpose: To determine the potential use and effectiveness of camwood as a source of bioactive ingredients in the pharmaceutical formulation of face cream, wash, toner and serum for dermatological use.

Methods: Following the International Nomenclature of Cosmetic Ingredients (INCI) guidelines, formulations were developed to ensure therapeutic efficacy and safety. As part of pre-formulation studies, organoleptic and physicochemical tests were carried to ensure safety and efficacy of the active ingredients. Multiple trial formulations were evaluated for consistency, spreadability, and sensory attributes to select the best formulations which were further evaluated for dermal toxicity. The final products were also subjected to the appropriate quality assurance testing.

Results: The selected formulations, characterized by their fruity odor, reddish orange color, and appropriate consistency, met all required parameters and also demonstrated significant potential in resolving hyperpigmentation, moisturizing the skin, improving appearance and texture without causing irritation, allergic reactions or adverse effects during appropriate evaluations under the right conditions. The face cream exhibited good spreadability, the face wash showed ideal foaming index for all skin types including sensitive skin. The toner exhibited the ability to remove residual dirt on the skin after cleansing while the serum was lightweight and fast absorbing. All four formulations showed depigmenting, skin-brightening, tightening of pores and hydrating abilities indicating their potential uses as a comprehensive pharmaceutical solution for improved dermatological health. Organoleptic and physicochemical evaluations affirmed their effectiveness in improving skin texture and radiance, underscoring the therapeutic potential of camwood-based dermaceuticals.

Conclusions: The development of camwood dermaceutical face cream, wash, toner and serum demonstrate the convergence of cosmetic appeal and clinical efficacy, offering a novel approach to dermatological health. Findings highlight the potential of safe natural ingredients in the formulation of sustainable, eco-friendly therapeutic personal care products and the critical role pharmacists play in facilitating access to innovative skincare solutions. These findings suggest further exploration into dermaceuticals as a sustainable and effective strategy in enhancing dermatological health and wellness.

The effect of natural Emu Oil on inflammation induced in full-thickness human skin

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Introduction: Several studies have shown the potential of Emu oil to reduce inflammation in gastrointestinal tract diseases Mashtoub et al, 2023). Only a few studies however have established the anti-inflammatory potential of Emu oil in disorders of the skin (Miyashita et al, 2018). The primary mediators of an inflammatory response include several cytokines, namely, interleukin-1beta (IL-1beta), interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor alpha (TNF-alpha). Initiation of the inflammatory process involves the activation and recruitment of macrophages, mast cells, endothelial cells, and Schwann cells which leads to the production and release of cytokines. Attenuation of these cytokines by Emu oil would indicate an anti-inflammatory response. This study aims to determine the anti-inflammatory potential of natural Emu oil in full-thickness ex vivo human skin explants.

Method: The anti-inflammatory potential of natural Emu oil was determined utilizing fresh full-thickness human skin explants with 0.5cm of fat (Gvirtz et al, 2020). The skin was punched to approximately 12mm (12-well) discs and placed in Transwell inserts with the epidermis side up in contact with air and dermal side submerged in the medium. Skin explants were cultured in Dubelco's Modified Eagles Media (DMEM) containing 265mg/L calcium, 5% fetal bovine serum (FBS), penicillin (100 IU/mL), streptomycin (100mcg/mL) and amphotericin B (0.125mg/mL) at 37°C, 5% CO₂. To determine the effects of Emu oil on lipopolysaccharides from *Escherichia coli* O111:B4 (LPS) induced inflammation, the culture medium was replaced with culture media containing LPS (1mcg/mL) and incubated for 24 hours. After 24 hours, the culture medium was replaced with culture media containing the test substances or applied topically to the skin. The skin explant was further incubated for 24 hours. After a 24-hr incubation period, the culture media was collected for analysis of cytokines. Test substances included skin alone (NT, no treatment), LPS follow by dexamethasone (DEX, known inhibitor), LPS follow by natural Emu oil (EO, replaced culture media or EOT, applied topically). The release of cytokines from the skin were measured using a Human Cytokine ELISA to quantitate IL-1beta, IL-6, IL-8 and TNF-alpha.

Result: IL-1beta, IL-6, IL-8 and TNF-alpha levels were significantly enhanced by the LPS stimuli, resulting in approximately 8-fold, 2.44-fold, 16.45-fold and 17.55-fold increase compared to no treatment, respectively. Dexamethasone placed in culture media attenuated LPS-induced cytokine production, however, this trend was found to be statistically significant only with regards to IL-8 and TNF-alpha. Natural Emu Oil significantly attenuated the hypersecretion of all cytokines except IL-1beta when placed in the culture media. If placed topically on the skin, natural

Emu oil significantly reduced the concentration of TNF-alpha and IL-8 produced because of LPS induction by 73% (3.5 to 0.94 pg/mL) and 13.3% (1225.38 to 1062.24 pg/mL), respectively.

Conclusion: Natural Emu oil has the potential to attenuate cytokines induced after an inflammatory response in the skin.

Ex vivo skin-permeation of ciclopirox olamine from different gels

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Background: Ciclopirox olamine is a lipophilic antifungal agent used in the treatment of skin and nail fungus. In the development of dermatological formulations, it is important to determine the influence of excipients on the penetration of active compounds into the skin layers. Emulgels are a semi-solid dosage form that has the properties of both hydrogels and emulsions. It is important to study the influence of oil phase components on the penetration of compounds into the skin. Mineral oil, isopropyl myristate and oleic acid were chosen as a lipophilic phase. Objectives: To determine the penetration of ciclopirox olamine into human skin from gels with different lipophilic agent and distribution between the epidermis and dermis.

Methods: Four different poloxamer 407 gels with 1% ciclopirox olamine and 30% polyethylene glycol 400 were prepared: without additional substances, with 10% mineral oil, with 10% oleic acid, with 10% isopropyl myristate. Ethics permission for research with human skin was obtained from the Kaunas Regional Bioethical Committee BE-2-42 (May 3, 2023). Ex vivo skin-permeation studies were performed using Bronaugh-type flow-through diffusion cells and Caucasian women's abdominal skin. The epidermis layer was separated from the dermis by heat treatment. The concentration of ciclopirox olamine was determined using Ultra-performance liquid chromatography validated method. Rheological properties of tested gels were determined using an MCR102 rotary rheometer and temperature ramp test.

Results: Rheological measurements showed that the complex viscosity of hydrogel was 2166.6–2599.7 Pa·s. The addition of oleic acid and mineral oil statistically significantly ($p < 0.01$) reduced complex viscosity values over the entire temperature range studied, while isopropyl myristate statistically significantly increased it. Ex vivo skin penetration studies revealed the flux of ciclopirox olamine from an aqueous 30% polyethylene glycol 400 solution into the epidermis was 73.7 (6.0) $\mu\text{g}/\text{cm}^2$, and into the dermis was 109.8 (26.1) $\mu\text{g}/\text{cm}^2$. The penetration into the epidermis from the tested gels was: hydrogel – 7.5 (4.6) $\mu\text{g}/\text{cm}^2$, with mineral oil – 7.0 (2.1) $\mu\text{g}/\text{cm}^2$, isopropyl

myristate – 10.9 (5.9) $\mu\text{g}/\text{cm}^2$, oleic acid – 11.9 (4.9) $\mu\text{g}/\text{cm}^2$. The penetration into the dermis from the tested gels was: hydrogel – 31.4 (16.1) $\mu\text{g}/\text{cm}^2$, with mineral oil – 30.2 (6.7) $\mu\text{g}/\text{cm}^2$, isopropyl myristate – 27.0 (11.0) $\mu\text{g}/\text{cm}^2$, oleic acid – 26.4 (10.2) $\mu\text{g}/\text{cm}^2$. There was not statistically significant ($p > 0.05$) difference in ciclopirox olamine fluxes into either the epidermis or dermis between the tested gels.

Conclusions: The complex viscosity of gels is affected by the type of oil chosen. However, the oil phase has no significant effect on the penetration and distribution of ciclopirox olamine between the epidermis and dermis. The rheological properties and composition of the tested gels do not affect the biopharmaceutical properties.

Multifunctional nanovesicle strategy for immune modulation and tumour-targeted therapy in metastatic melanoma

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Introduction: Metastatic melanoma (MM) is an aggressive malignancy with limited treatment options. Current chemotherapy, radiotherapy, and immunotherapy approaches exhibit significant limitations. However, MM's strong immunogenicity and active immune cell infiltration provide a promising avenue for eliciting tumour-specific immune responses. Developing effective therapeutic strategies to activate MM-associated immune cells is therefore critical for overcoming treatment challenges. This study aims to develop a multifunctional targeted drug delivery system (GNVs-Ab/TP-Pro), which is constructed using ginseng-derived nanovesicles (GNVs) encapsulating the triptolide prodrug (TP-Pro) and functionalised with a single-chain antibody targeting melanoma-associated chondroitin sulphate proteoglycan (MCSP). This system is designed to reverse the immunosuppressive tumour microenvironment (TME), induce tumour cell apoptosis, and block metastatic signalling pathways, thereby achieving a synergistic anti-tumour effect through multiple mechanisms.

Methods:

1. Preparation and Characterisation: GNVs were extracted via ultracentrifugation, TP-Pro was encapsulated through cyclic sonication, and MCSP-scAb was conjugated to construct GNVs-Ab/TP-Pro. Physicochemical properties, including size, zeta potential, encapsulation efficiency, and stability, were assessed.

2. In Vitro Evaluation: The cytotoxicity, apoptosis-inducing capacity, and 3D tumour spheroid penetration ability of GNVs-Ab/TP-Pro were assessed. The system's anti-metastatic effects were evaluated via invasion and migration assays. Western blot analysis was conducted to elucidate the cooperative mechanisms of MCSP-scAb and TP-Pro.

3. In Vivo Assessment: An A375M xenograft model in nude mice was established. Tumour volume and weight reductions, along with HE, TUNEL, and Ki67 staining, assessed anti-tumour efficacy. Modulation of the TME, including macrophage polarisation reversal, immunogenic cell death (ICD) induction, dendritic cell maturation, and T-cell infiltration, was examined. Body weight, organ indices, haematological and biochemical indices, and histopathological analysis evaluated systemic safety.

Results:

1. Physicochemical Characterisation: Uniform-sized GNVs were successfully extracted. After TP-Pro loading, GNVs/TP-Pro achieved an encapsulation efficiency of $41.76 \pm 0.56\%$ and a drug-loading capacity of $7.60 \pm 0.09\%$. MCSP-scAb was prepared, and interaction assays confirmed its high affinity for MCSP. The optimal conjugation ratio of GNVs/TP-Pro to MCSP-scAb was 10:1, yielding GNVs-Ab/TP-Pro with a mean particle size of 127.10 ± 0.56 nm.

2. Enhanced In Vitro Anti-tumour Activity: GNVs-Ab/TP-Pro demonstrated the highest cytotoxicity ($\text{IC}_{50} = 55.93$ $\mu\text{g}/\text{mL}$) and apoptosis rate ($68.04 \pm 2.26\%$). 3D tumour spheroid assays revealed enhanced penetration and apoptosis induction. Furthermore, MCSP-scAb and TP-Pro synergistically suppressed invasion and migration. Mechanistically, TP-Pro activated caspase pathways and inhibited JAK2/STAT3 signalling, while MCSP-scAb suppressed focal adhesion kinase (FAK) and MAPK pathways, reducing tumour cell migration and invasion.

3. Superior In Vivo Efficacy and Safety: In A375M xenografts, GNVs-Ab/TP-Pro displayed the most potent anti-tumour activity. It significantly reversed M2 macrophage polarisation, induced ICD, and promoted dendritic cell maturation. Safety evaluations revealed that GNVs-Ab/TP-Pro exhibited low systemic toxicity, with organ histology, haematology, and biochemical indices comparable to control groups.

Conclusion: This study develops a novel multifunctional targeted drug delivery system, utilising GNVs for immune modulation and TP-Pro for tumour eradication in MM therapy. The engineered system successfully achieved multi-pathway synergistic tumour suppression, demonstrating potent anti-tumour efficacy and favourable safety profiles in animal models. This strategy offers a promising framework for advancing nanocarrier-based anti-tumour therapies with significant clinical translation potential.

Application of solid-lipid nanoparticles and pegylated solid dispersions to enhance delivery of nevirapine for HIV/AIDS management

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Introduction: Nevirapine is a non-nucleoside reverse transcriptase inhibitor that is used with other antiviral drugs in the management of HIV/AIDS especially in the prevention of mother-to-child transmission. Extended release paediatric suspensions of Nevirapine reduces dosing frequency and improves patient compliance. The preparation and assessment of PEGylated Solid Dispersions (SD) and Solid Lipid Nanoparticles (SLNs) of nevirapine with improved oral delivery for better management of HIV/AIDS was the aim of this research.

Methods: Four batches of nevirapine physical mixtures (PM) and three batches of solid dispersions (SD) of nevirapine comprising diverse ratios (1:0, 1:0.5, 1:1 and 1:2) of nevirapine/ PEG 4000 were prepared and their granules and tablets screened for micromeritics properties and tablet properties. Twenty-one batches of SLNs of nevirapine were also produced from dika wax and evaluated for distribution of the sizes of particles, surface shape and charges, in vitro drug release properties, etc.

Results: From the results obtained, it can be said that all batches of granules prepared had poor flow. However, the granules prepared by solid dispersion method showed better flow properties than those prepared by physical mixture method. All the tablet batches passed weight uniformity. Disintegration and hardness tests, though batches PM1 and SD1 failed friability test. The SD tablets had higher dissolution efficiencies than the PM tablets with SD3 tablets standing out as the best batch. Cryo-TEM results revealed that the SLNs are round to oval in shape with smooth external surface. Zeta sizer particle sizes and distribution analysis indicated quality results for Nevirapine SLN Batches 15 and 18. The zeta potential results were: -16.83 ± 0.404 mV for Batch 1, -44.30 ± 0.624 mV for Batch 15 and -40.03 ± 2.65 mV for Batch 18. Batches 15 and 18 SLNs had loading capacities of 6.71% and 9.82% respectively and encapsulation efficiencies of 49.35%

and 70.19% respectively. In vitro dissolution showed 102% release for batch 18 and 87.5% release for Batch 15 with a dissolution efficiency of 65% for Batch 15 and 83% for Batch 18 SLNs. f2 statistic revealed that Batch 6 SLNs are similar to Batch 15 SLNs while Batch 15 SLNs are similar to Batch 18 SLN.

Conclusion: Batch SD-3 PEGylated solid dispersions and Batches 15 and 18 SLNs have good properties for enhancing the delivery of nevirapine as extended release dosage forms for better management of HIV/AIDS.

Enhancing targeted liver fibrosis therapy: Evaluating retinol-modified nanoparticles for Activated Hepatic Stellate Cells targeting and assessing atorvastatin- and JQ1-loaded NPs for effective aHSC deactivation

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Background: Fibrotic diseases impose a substantial burden on healthcare systems. Liver fibrosis, a precursor to cirrhosis, stands as the 11th most significant contributor to global mortality. While the reversal of liver fibrosis is now considered an attainable objective, the absence of an anti-fibrotic drug in the market remains a significant challenge. Numerous agents such as statins and BRD4 inhibitors exhibit promise in halting and reversing the activation of activated hepatic stellate cells (aHSCs), the pivotal contributors to fibrosis progression. However, these agents often face limitations such as inadequate solubility, high toxicity, extensive side effects, and non-specific distribution throughout the body following systemic administration. Nanoparticle-based drug delivery systems offer potential solutions to such limitations.

Methods: Chitosan nanoparticles (NPs) (150 nm) were synthesized using ionotropic gelation and loaded with atorvastatin (AS) and JQ1. Encapsulation efficiency (EE%) was quantified using UPLC-MS/MS and spectrophotometry, respectively. Surface modification with retinol (Rt) was achieved using 1,1-Carbonyldiimidazole as a crosslinker, with tagged Rt molecules quantified by fluorometry. Fluorescein-labeled Rt-NPs were used to evaluate uptake in GRX cells (aHSC model) via fluorometry. Western blot analysis assessed aHSC deactivation by quantifying fibronectin, vimentin, and PDGFR- β expression following GRX treatment with free drugs, unmodified NPs (JQ1-NPs, AS-NPs), and Rt-modified NPs (Rt-JQ1-NPs, Rt-AS-NPs). In vivo, Rt-NPs biodistribution was evaluated in Swiss albino mice with carbon tetrachloride (CCl₄)-induced liver fibrosis following three intravenous (IV) injections. Fluorescence quantification in organ homogenates determined NP accumulation.

Results: NPs were successfully functionalized with high density retinol (26822 Rt/NP). These Rt-NPs exhibited preferential uptake by GRX cells compared to unmodified NPs. The uptake mechanism was proposed to involve receptor-mediated endocytosis, as indicated by the reduced uptake extent when the cells were pre-treated with excess free retinol. Subsequently, AS and JQ1 were successfully loaded into the NPs and Rt-NPs, resulting in 68% and 84% EE% for AS and JQ1, respectively. Both Rt-AS-NPs and Rt-JQ1-NPs exhibited significant potential in deactivating aHSCs, characterized by reduced expression of fibronectin, vimentin, and PDGFR- β —markers associated with fibrosis progression. Notably, the effect exerted by Rt-AS-NPs and Rt-JQ1-NPs was more pronounced than that observed with AS-NPs, JQ1-NPs, or either of the free drugs. Furthermore, the combination treatment using Rt-AS-NPs and Rt-JQ1-NPs demonstrated a remarkably significant reduction in all fibrosis-associated markers compared to all other tested formulations. Additionally, *in vivo*, retinol functionalization significantly enhanced NP accumulation in fibrotic livers compared to healthy controls. Biodistribution analysis confirmed liver-specific targeting, with reduced accumulation in the kidneys, heart, and brain, indicating improved specificity and minimizing off-target effects.

Conclusion: The introduction of retinol on NPs enhanced their specificity and targeting capability, as evidenced by increased uptake both *in vitro* and *in vivo*. Furthermore, loading AS and JQ1 into chitosan NPs improved their cellular tolerability and addressed the low solubility issue of both drugs. The synergistic action of Rt-AS-NPs and Rt-JQ1-NPs to reverse the activation of aHSCs, suggests a promising targeted therapeutic strategy for fibrotic disorders, particularly liver fibrosis.

Enhanced solubility and membrane permeability by coamorphous nanoparticles via co-precipitation of two drugs

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Introduction: Coamorphous solids represent an amorphous state in stoichiometric binary systems composed of a drug and a compatible coformer. The formation of coamorphous systems contributes to improving the solubility and oral absorption of target drugs. Typically, dry milling and spray drying are employed to produce coamorphous particles. However, these methods often result in particle sizes in the micrometre range. It has been reported that nanoparticles can penetrate deeply into the intestinal membrane through the unstirred water layer, thereby enhancing drug permeability. In this study, coamorphous nanoparticles were prepared via the co-precipitation of two drugs. The impact of

coamorphous nanoparticle formation on solubility and membrane permeability was investigated.

Method: Atorvastatin calcium hydrate (ATC) and nifedipine (NDP) were used as model drugs. ATC and NDP were dissolved in methanol at molar ratios of 2:1, 1:1, and 1:2. The methanolic drug solution was added into PVA aqueous solution. The resulting dispersion was immediately centrifuged at 4°C and 50,000 rpm for 10 minutes. The obtained residue was then redispersed in distilled water with sonication, and the final dispersion was subjected to freeze-drying. The crystallinity of the freeze-dried powder was evaluated using powder X-ray diffraction. The particle size of the freeze-dried samples, after dispersion in distilled water, was determined using dynamic light scattering with a Litesizer 500. The phase behaviour of supersaturated drug solutions was assessed using the μ DISS system. The solubility and permeability of the drugs were evaluated using the μ Flux system, with the test concentration set at 50 μ g/mL based on the NDP concentration.

Results: When the methanolic solution of either ATC or NDP alone was added to the aqueous solution, their particle sizes remained in the micrometre range. The combination of ATC and NDP resulted in a reduction of both drugs to the nanometre range. Notably, the NDP:ATC (1:2) formulation maintained nanoparticle stability without aggregation after freeze-drying. All freeze-dried powders (FDPs) of NDP:ATC and ATC alone exhibited an amorphous state. In contrast, the FDPs of NDP alone showed crystalline peaks originating from NDP. To investigate the phase behaviour of supersaturated solutions, UV measurements were conducted in a PVA solution using the μ DISS system. The precipitation concentration of ATC remained constant in all ratios, whereas NDP was found to precipitate at the same concentration as ATC. These findings suggested that the coamorphous nanoparticles is formed by the co-precipitates between ATC and NDP. The dissolution and permeability of both drugs were evaluated using the μ Flux system. Untreated NDP powder exhibited a low dissolution rate and a low NDP concentration in the donor chamber, resulting in minimal permeation of NDP into the acceptor chamber. In contrast, FDPs of NDP:ATC (1:2) maintained NDP supersaturation in the donor chamber, leading to a fourfold increase in the permeated amount of NDP compared to untreated NDP powder.

Real-world utilisation, efficacy, and safety of injectable GLP-1 receptor agonists: A drug use evaluation in Singapore's largest healthcare cluster

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Introduction: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as essential therapies in the management of type 2 diabetes mellitus (T2DM) and obesity. This study aimed to conduct a comprehensive drug use evaluation (DUE) of injectable GLP-1RAs within Singapore's largest healthcare cluster, focusing on the appropriateness of indication, efficacy in weight loss and glycemic control, and safety profile.

Method: A retrospective review of medical records was conducted for patients prescribed injectable GLP-1RAs (dulaglutide, liraglutide, or semaglutide) between July 2022 and June 2023 across SingHealth institutions. Appropriateness of indication was assessed against approved criteria. Efficacy was evaluated by changes in HbA1c for type 2 diabetes mellitus (T2DM) patients and body weight for those receiving treatment for weight loss. Safety was assessed by reviewing documented adverse events. Logistic regression analyses identified predictors of efficacy and safety.

Results: Among 915 patients included, the majority were female (53.3%), aged 35–64 years (74.4%), and had obesity (80%). Appropriate prescribing rates were 96.3%, primarily for weight loss (65.2%) and T2DM (31.0%). Efficacy analysis showed 51.3% of patients achieved $\geq 5\%$ weight reduction, while 58.7% attained $\geq 1.0\%$ HbA1c reduction. Adverse events were reported in 37.9% of patients, predominantly gastrointestinal symptoms. Factors influencing outcomes included treatment duration, GLP-1RA type, and baseline clinical parameters.

Conclusion: The DUE affirmed the appropriateness, efficacy, and safety of injectable GLP-1RAs for weight loss and T2DM management in a real-world setting. The findings provide actionable insights to optimise GLP-1RA utilisation and improve patient outcomes, emphasising the importance of patient selection, monitoring, and education in maximising therapeutic benefits.

In vitro release and safety study of the synthesized syringic acid loaded MIL-100(Fe) and modified MIL-100(Fe)

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Phenolic acids like syringic acid possess antioxidant and antimicrobial properties but face challenges in bioavailability. Advances in drug delivery, particularly metal-organic frameworks (MOFs) like MIL-100(Fe), offer solutions by improving stability, controlled release, and bioavailability. Thus, in this study, MIL-100(Fe) was synthesized by substituting trimesic acid with syringic acid at varying molar concentrations. Both pristine and modified MIL-100(Fe) were prepared, and syringic acid was loaded via simple impregnation at 12, 24, 36, and 48 hours, using 1:1 and 1:2 ratios. The synthesized materials were characterized using Powder X-Ray Diffraction (PXRD), Nitrogen Adsorption-Desorption analysis, and Fourier Transform Infrared Spectroscopy (FTIR). An in vitro and in vivo toxicity study evaluated the biocompatibility of syringic acid-loaded MIL-100(Fe).

The study revealed that independent variables, including loading time, syringic acid-to-MIL-100(Fe) ratio, and framework modification, significantly influenced the mean drug loading percentages ($p < 0.001$). The highest mean drug loading percentages were observed at 12 hours ($64.42 \pm 0.03\%$) for the 1:1 ratio and 36 hours ($26.38 \pm 0.02\%$) for the 1:2 ratio in pristine MIL-100(Fe). For modified MIL-100(Fe), the highest loading percentages were at 36 hours, with values of $33.70 \pm 0.00\%$ (1:1 ratio) and $66.85 \pm 0.00\%$ (1:2 ratio). The loading of syringic acid to the framework did not result in a specific trend. PXRD, Nitrogen Adsorption-Desorption, and FTIR results confirmed the successful entrapment of syringic acid in both pristine and modified MIL-100(Fe).

The release kinetics of syringic acid from the frameworks were modeled in various media, including water, phosphate-buffered saline (PBS) at pH 7.4, pH 6.8, and 0.1 N HCl at pH 2. The Higuchi model provided the best fit for the release profiles, suggesting that the release of syringic acid in MIL-100(Fe) and modified MIL-100(Fe) is mainly driven by diffusion-controlled mechanism, and through the Korsmeyer-peppas model, it suggests a case 1 diffusion (Fickian Diffusion). Based on the OECD 423 guidelines, both preparations were considered non-toxic, and serological data of the AST, ALT, BUN, and Creatinine levels were drastically reduced pre- and post-administration of the preparation.

The study successfully synthesized and characterized pristine and modified MIL-100(Fe) frameworks, demonstrating their potential as drug carriers for syringic acid. The high surface area and versatile structural properties of MIL-100(Fe) make it a promising candidate for future therapeutic applications, particularly for drug delivery systems.

Design of spray dried cyclodextrin-metal organic framework particles containing hydrophobic and hydrophilic compounds

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Introduction: Cyclodextrin-based metal-organic Framework (CD-MOF), coordination compounds with good biocompatibility, are attracting interest as porous nano-carriers. The CD-MOF particle is generally prepared by a vapour diffusion and anti-solvent crystallisation method; however, this process needs several days to weeks and has a low yield of drug content. This research focuses on the design of drugs containing CD-MOFs by spray drying. We hypothesise that amorphous to crystal phase transition during the spray drying process lead to formation of CD-MOF. The purpose were, (i) to produce the high drug loading CD-MOFs in short time by spray drying, (ii) to characterise the morphological and crystalline state of dried particles, (iii) to understand the spatial distribution of hydrophobic and hydrophilic drugs in the particles.

Method: Etodolac (ETD; hydrophobic drug) and anhydrous theophylline (THP; hydrophilic drug) were selected as model compounds. γ -CD and KOH was completely dissolved in water at a 1:8 molar ratio. Following the addition of ethanol (40% v/v), the mixture was stirred and processed by anti-solvent crystallisation method or spray drying (SD). In procedure of drug-containing particles, THP and ETD were added and dissolved in initial water and ethanol, respectively. The obtained dried particles were subjected to morphological analysis, powder X-ray diffraction (XRD), and Raman imaging microscopy. The dissolution testing was performed in water (37°C).

Results: Over 90% drug-containing CD-MOF particles were produced in 30 min by spray drying (SD); high drug loading and drastic time reduction were simultaneously accomplished. SEM image and BET analysis revealed that SD particle shows micro-spherical shape, and especially ETD containing particle was characterised formation of cubic

crystal on the surface and an increase of specific surface area due to the growth of CD-MOF crystal. The XRD pattern of the particle exhibit peaks of CD-MOF (4°, 7°, and 14° 2 θ), and no peaks of drugs. The amorphised THP and ETD showed immediate release profiles in water. Furthermore, the structure of CD-MOF was stabilised by presence of these drugs under 40°C/75% RH condition. Spray-dried CD-MOF formed low-density pores in the centre and linker section in the (γ -CD)⁶ crystal for the containing of drug molecules with stabilised state. Additionally, Raman imaging confirmed that ETD and THP were dispersed homogeneously in the microspheres.

Conclusion: The formation of cyclodextrin-metal organic framework (CD-MOF) particles containing THP and/or ETD with high loading were successfully demonstrated by spray drying. The synthesized time and drug content were significantly improved compared with the general anti-solvent crystallisation method. Spray drying is adaptable for large-scale manufacturing, the proposed efficient methodology to prepare drug containing CD-MOFs has a potential to be utilised in the pharmaceutical industry.

Artificial intelligence application for emulsion design and optimization utilising Microfluidics

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Introduction: Artificial intelligence (AI) has shown high success when implemented in various pharmaceutical applications. Moreover, microfluidics is a technique that has promising potentials to produce monodispersed oil-in-water (O/W) and water-in-oil (W/O) emulsions. The stability of an emulsion is important in which a uniform composition is maintained, and the separation of its components is prevented during storage. This work aims to develop an AI application utilising artificial neural networks (ANNs) that can predict the droplet sizes in different emulsions generated using different oils by microfluidics.

Method: ANNs were utilised as an AI technique to model microfluidic systems using various oils. The ANN was trained using numerous experimental conditions of microfluidic systems such as flow rates.

Results: The preliminary results showed that the developed ANN could provide highly accurate predictions of different droplet sizes in emulsion systems generated by different oils utilising microfluidics.

Conclusion: Integrating artificial intelligence and microfluidics may offer promising opportunities for developing optimised emulsion systems with long-term storage stability.

Expression and localisation of organic anion transporting polypeptide (Oatp) 2b1 in the term rat placenta

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Introduction: During pregnancy, drugs transfer to the fetus through the placental barrier, which consists of layers of syncytiotrophoblasts (SynT). SynT expresses drug transporters that play a crucial role in the placental transfer of drugs. The structure of SynT varies across species; in humans, it consists of a single layer, whereas in rodents, it comprises two distinct layers: SynT-I, located on the maternal side, and SynT-II, on the fetal side. Oatp2b1, an organic anion-transporting polypeptide expressed in the human placenta, has been suggested to facilitate the placental permeation of angiotensin II receptor antagonists (ARBs) and other drugs. Since ARBs are contraindicated during pregnancy due to their association with fetal toxicity, such as oligohydramnios, understanding the expression and function of Oatp2b1 is essential for assessing their pharmacological and toxicological effects on the fetus. To extrapolate drug transfer data from rodent models to humans, this study investigated the expression and localisation of Oatp2b1 in the rat placenta.

Methods: Rat placentas were collected at gestational day 20.5 and divided into three regions: the labyrinth, which contains SynT, as well as the decidua and the junctional zone. Oatp2b1 mRNA and protein expression levels were analysed using quantitative RT-PCR and Western blotting. To study Oatp2b1 function, a Flp-In T-REx 293 cell line was genetically modified to conditionally express rat Oatp2b1. Additionally, a novel anti-rat Oatp2b1 antibody was generated by immunising rabbits. Localisation of Oatp2b1 was evaluated using single immunostaining with the anti-Oatp2b1 antibody. Double immunohistochemistry was performed using Cx26, a marker for the connection between SynT-I and SynT-II, and GLUT1, a marker for the maternal-facing plasma membrane in SynT-I and the fetal-facing plasma membrane in SynT-II.

Results: Oatp2b1 mRNA expression in the placental labyrinth was approximately 5.5 times higher than in the decidua/junctional zone. Western blot analysis identified Oatp2b1 protein in the plasma membrane fraction of placental tissue at approximately 90 kDa, consistent with its

expression in rat Oatp2b1-expressing cells. Immunohistochemistry revealed a strong Oatp2b1 signal in the labyrinth, whereas its expression was significantly lower in other placental regions. These results suggest that Oatp2b1 expression is predominantly concentrated in the labyrinth, which serves as the primary site of maternal-fetal exchange. Furthermore, Oatp2b1 immunostaining in the labyrinth did not overlap with GLUT1 staining in the maternal plasma membrane of SynT-I cells but showed partial overlap with GLUT1 staining in the fetal plasma membrane of SynT-II. Additionally, Oatp2b1 staining overlapped with Cx26 in the placental labyrinth, indicating its presence at the interface between SynT-I and SynT-II.

Conclusion: In full-term pregnant rats, Oatp2b1 mRNA and protein are highly expressed in the placental labyrinth, where the placental barrier is located. The localisation of Oatp2b1 at the placental barrier suggests its presence in the plasma membrane, potentially contributing to placental drug transport. These findings provide valuable insights into placental drug transfer mechanisms and may help in predicting drug transport across the placenta in rodent models and extrapolating these findings to humans.

Differences in the KATP channel-independent and endothelium-independent effects of pinacidil on bypass grafts from patients with type 2 diabetes mellitus

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Background: Type 2 diabetes mellitus (T2DM) is one of the main risk factors for cardiovascular complications. The reduced relaxation of blood vessels in diabetic patients may be due to altered expression and/or function of smooth muscle potassium (K) channels. Previously, we have shown that pinacidil, an ATP-sensitive K (KATP) channel opener, has vasodilatory effects on bypass grafts that are independent of KATP channel activation.

Purpose: Therefore, the aim of our study was to investigate the differences in the involvement of voltage-gated K (Kv) and large-conductance Ca-sensitive K (BKCa) channels in the effects of pinacidil on human saphenous veins (HSV) and human internal mammary arteries (HIMA) from patients with T2DM.

Method: Rings of HSV and HIMA obtained from patients during bypass surgery without endothelium were mounted in an organ bath system and isometric tension was recorded. Relaxation of HSV and HIMA precontracted with

phenylephrine and serotonin, respectively, was induced by pinacidil.

Results: Pinacidil produced concentration-dependent relaxation of HSV and HIMA from T2DM patients. 4-aminopyridine (4-AP, 1mM and 3mM), non-selective blocker of Kv channels, did not antagonize pinacidil effects on HSV from T2DM patients. However, 4-AP (3 mM) antagonized pinacidil effects on HIMA from T2DM patients ($P < 0.05$). Margatoxin, specific blocker of Kv1 channels, and iberiotoxin, specific blocker of BKCa channels did not antagonize pinacidil effects neither on HSV nor on HIMA from T2DM patients.

Conclusion: Pinacidil causes comparable relaxation of HSV and HIMA in patients with T2DM. 4-AP-sensitive Kv channels are likely involved in pinacidil-induced relaxation of HIMA from T2DM patients. However, in patients with T2DM, 4-AP-sensitive Kv channels were not involved in the pinacidil effects on HSV. Based on the results obtained with margatoxin and iberiotoxin, it appears that Kv1 and BKCa channels are not involved in the pinacidil effects on HSV and HIMA from patients with T2DM.

Nose-to-brain delivery of cholecalciferol nanoparticles: A promising first-aid therapy for ischemic stroke

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Introduction: Ischemic stroke represents a global healthcare challenge, particularly with an aging population and a rise in chronic conditions. It remains a leading cause of mortality and long-term disability. Current therapeutic interventions, such as tissue plasminogen activator and endovascular thrombectomy, are constrained by issues related to accessibility and the need for rapid administration. There is an unmet need for innovative and user-friendly first-aid therapies for ischemic stroke. Cholecalciferol (VitD3) has emerged as a promising candidate due to its multi-target and multi-phase neuroprotective effects. The integration of nanotechnology with nose-to-brain delivery facilitates the rapid, efficient, and targeted delivery of VitD3 to the brain, offering an accessible and advanced solution to address the current clinical limitations in treating ischemic stroke.

Method: The VitD3 nanosuspension was fabricated using flash nanoprecipitation. D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS) and cholesterol (CLT) were employed as stabilizers in a VitD3:TPGS:CLT ratio of 50:1:0.2 (w/w/w). Particle size and polydispersity index (PDI) were measured using dynamic light scattering. Physical stability was

monitored based on criteria of particle size change $< 20\%$ and PDI change < 0.3 . The encapsulation efficiency (EE) was determined using an HPLC. The morphology was examined using Transmission Electron Microscopy (TEM). In vitro cytotoxicity was assessed on SH-SY5Y cells using the CCK-8 assay. In vivo efficacy was evaluated in C57BL/6 mice using the middle cerebral artery occlusion model induced by electrocoagulation. The treatment group (MCAO+NP) received intranasal liquid instillation of the nanosuspension (2 mg/kg of VitD3) at 30 minutes post-surgery ($n=5$). For comparison, a sham-operated group (sham) and an untreated group (MCAO) were included. Neurological recovery was assessed after 24 hours post-surgery using various behavioural tests, including adhesive removal test, balance beam test, and rotarod test. Subsequently, brain tissue was harvested for histological analysis, with brain slices prepared via paraffin sectioning and Nissl staining.

Results: The VitD3 nanosuspension exhibited a particle size of 133.63 ± 1.27 nm, a PDI of 0.17 ± 0.03 , physical stability of 208.0 ± 29.9 hours, and an EE exceeding 99.99%. TEM images revealed that the nanoparticles were spherical. No cytotoxicity of nanosuspension was observed within the concentration range of 6.25 to 25 $\mu\text{g/mL}$. In both the adhesive removal test and the balance beam test, the mice in MCAO+NP group removed the adhesive tapes and traversed the beam in a time comparable to the sham group and significantly shorter than the MCAO group ($p < 0.0001$, One-way ANOVA). In the rotarod test, the mice in MCAO+NP group remained on the rotarod for a significantly longer duration than the MCAO group ($p < 0.001$, One-way ANOVA). Histological analysis of brain slices indicated that the infarct size was markedly reduced in the MCAO+NP group compared to the MCAO group.

Conclusion: The VitD3 nanosuspension was successfully fabricated with acceptable stability, superior EE and negligible cytotoxicity. The nose-to-brain delivery of VitD3 nanoparticles as a first-aid therapy effectively safeguarded neurons in diseased mice, resulting in reduced brain infarct volume and preserved motor function. This innovative approach holds significant potential for transforming the treatment paradigm in ischemic stroke.

The role of microRNAs in the treatment of multiforme glioblastoma: A systematic review

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Background: Glioblastoma multiforme (GBM), also referred to as a grade IV astrocytoma, is an aggressive primary malignant brain tumor in adults. It is highly lethal and exhibits strong resistance to conventional therapies. Radiotherapy and chemotherapy have limited impact on patient's prognosis, underscoring the clinical challenge posed by GBM, which remains one of the most complex and treatment-refractory malignancies in oncology. MicroRNAs (miRNAs) are small non-coding RNAs involved in several critical biological functions in GBM, including tumorigenesis, invasion, angiogenesis and glioma stem cell behavior. Therefore, miRNAs are of great importance to GBM development and progression. Purpose: This systematic review aims to assess the role of miRNAs in GBM and how regulating their expression can enhance conventional treatments.

Methods: A systematic search was conducted in PubMed, Embase, and ScienceDirect for studies published between 2020 and 2025. The following search string was used: (glioblastoma OR "glioblastoma multiforme" OR "GBM") AND ("stem cells" OR "mesenchymal stem cells" OR "neural stem cells" OR "progenitor cells") AND ("microRNA" OR "miRNA" OR "microRNAs" OR "miR") AND ("therapy" OR "treatment" OR "therapeutic") AND ("combination" OR "synergism" OR "co-delivery" OR "dual approach"). Reference management and article screening were performed using EndNote X7 software.

Results: The ten selected studies identified several key miRNAs as critical regulators of GBM pathophysiology and treatment response. Tumor-suppressive miRNAs, including miR-124, miR-128, and miR-302a, were found to be downregulated in GBM, promoting glioma stem-like cell (GSC) differentiation and enhancing sensitivity to chemotherapeutic agents such as axitinib. The combination of miR-34a with suicide gene therapy demonstrated strong antitumor effects in vivo. Additionally, circulating miR-362-3p and miR-6721-5p were highlighted as non-invasive biomarkers with diagnostic value for glioma grading. In contrast, oncogenic miRNAs, including miR-10b, miR-21, and miR-425-5p, were consistently upregulated, contributing to GSC survival, proliferation, and treatment resistance.

Conclusion: MicroRNAs play a central role in the regulation of GSCs, influencing tumor growth, resistance mechanisms, and differentiation capacity. Their dual function as oncogenic or tumor-suppressive molecules makes them attractive therapeutic targets. This systematic review highlights the potential of using miRNAs not only as biomarkers but also as therapeutic tools. The results evidence that miRNAs modulation by restoring tumor-suppressive miRNAs or inhibiting oncogenic miRNAs is a promising strategy in GBM therapy, especially in combination with CAR-T cells or targeted agents.

Enhancement of alpha-lipoic acid solubility through cyclodextrin ternary complexation for improved therapeutic efficacy

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Alpha-lipoic acid (ALA) holds considerable therapeutic promise for treating obesity and its associated comorbidities, such as diabetic neuropathy and hyperlipidemia. However, achieving effective therapeutic doses requires high daily amounts (up to 1800 mg) due to ALA's poor bioavailability, which results primarily from its low solubility and gastrointestinal instability. These challenges contribute to increased therapy costs and decreased patient adherence. This study aimed to enhance ALA's solubility through the development of innovative pharmaceutical formulations utilizing cyclodextrin (CD) ternary complexes.

Building on our previous research, hydroxypropylated beta-CD was selected as the CD of choice. A total of 17 different ternary components commonly used to improve drug solubility—comprising amino acids, organic acids, and polymers—were tested. Differential scanning calorimetry (DSC) and isothermal stress testing were performed to identify ternary components compatible with ALA. A phase solubility study was then conducted to determine the ternary component with the greatest potential for enhancing ALA solubility in formulations containing hydroxypropylated beta-CD.

The results revealed compatibility with several amino acids (lysine, aspartic acid, and glutamic acid), one organic acid (malic acid), and two polymers (hydroxypropylmethylcellulose and hyaluronic acid), which were selected for further investigation. In contrast, four amino acids (glycine, cysteine, proline, and arginine), two organic acids (tartaric and succinic acid), and several polymers (polyvinylpyrrolidone, chitosan, polyethylene glycol, and poloxamer) were found to be incompatible with ALA. The phase solubility study among the compatible components identified the most promising ternary complex

for improving ALA solubility, demonstrating enhanced performance compared to binary CD complexes.

Cyclodextrin ternary complexation presents an effective strategy to improve ALA's bioavailability. This approach could reduce the necessary daily dose, thereby improving patient adherence and lowering therapy costs. Cyclodextrin ternary formulations offer a promising method to optimize ALA's therapeutic potential in obesity and its related comorbidities.

Improving the solubility and bioavailability of alpha-lipoic acid via hydroxypropyl-β-cyclodextrin complexation

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Alpha-lipoic acid (ALA) exhibits significant therapeutic potential in the management of obesity and its associated comorbidities, including diabetic neuropathy and hyperlipidemia. However, its clinical application is limited by poor oral bioavailability, primarily attributed to its low aqueous solubility and gastrointestinal instability. Consequently, high daily doses (up to 1800 mg) are required to achieve therapeutic efficacy, which may lead to increased treatment costs and reduced patient adherence.

This study aimed to enhance the solubility of ALA through the formulation of inclusion complexes with hydroxypropyl-β-cyclodextrin (HPβCD). Solid-state complexes were prepared via lyophilization and characterized using differential scanning calorimetry (DSC) and Fourier-transform infrared spectroscopy (FTIR). In vitro dissolution studies were conducted to evaluate the solubility enhancement, and permeability was assessed using a biomimetic membrane model.

The results confirmed successful complexation of ALA with HPβCD. Notably, the inclusion complex exhibited a significantly improved dissolution profile, particularly under simulated gastric conditions (pH 1.5). However, a modest reduction in membrane permeability was observed for the complex compared to free ALA.

Overall, cyclodextrin complexation appears to be a promising strategy to enhance the solubility and potentially the bioavailability of ALA. By improving its dissolution behavior, this approach may enable dose reduction, thereby improving patient compliance and reducing overall treatment costs. HPβCD-based formulations could play a pivotal role in maximizing the therapeutic potential of ALA in obesity and related metabolic disorders.

Modulation of P-glycoprotein expression and function in microglia: A drug barrier beyond the blood-brain barrier?

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Background: Microglia, as the resident immune cells of the brain are involved in the initiation of inflammatory responses due to neurological disorders such as Alzheimer's disease (AD). Microglia have functional drug transporters, including P-glycoprotein (P-gp), which can be compromised functionally due to the inflammatory activation of these cells. P-gp is a critical transporter for drug development given its numerous drug substrates, but also has a role in amyloid-β clearance in AD. The microglial inflammatory response can be regulated by key proteins such as fatty acid-binding protein 4 (FABP4), with FABP4 inhibition shown to reduce the inflammatory response to lipopolysaccharide (LPS). However, the effect of this anti-inflammatory action on microglial transporters remains unknown. This is important to characterise given the potential for microglial drug transporters to act as a secondary barrier to drug disposition within the central nervous system.

Methods: Murine microglia (BV-2 cells) were exposed for 24 hours to LPS (1 µg/mL) to model a generalised inflammatory response. Microglial transporter abundance was confirmed via quantitative targeted absolute proteomics (QTAP) and via western blot. BMS309403 (50 µM) was used to inhibit FABP4 in the presence of LPS, and the abundance of P-gp and other transporters was measured by QTAP. Gene expression for P-gp was determined by a quantitative polymerase chain reaction (qPCR).

Results: LPS treatment confirmed a reduction in microglial efflux transporter abundance, including P-gp (~32%), whilst demonstrating an upregulation of solute carriers such as organic anion transporting polypeptide 4a1 (↑29%). However, despite its anti-inflammatory actions, BMS309403 co-treatment with LPS did not reverse these LPS-mediated changes to microglial transporters. Interestingly, BMS309403 treatment on its own reduced P-gp abundance (~44%). Gene expression analysis via qPCR subsequently demonstrated that BMS309403 impacts P-gp transcription, with a reduction in

Abcb1b expression (~2-fold) observed after 24 hours exposure to the FABP4 inhibitor.

Conclusion: FABP4 inhibition in microglia can attenuate the microglial inflammatory response, although this does not lead to the restoration of implicated drug transporters. However, results obtained may yield a potential new regulatory mechanism through FABP4 for key drug transporters, which may assist in the therapeutic targeting of microglia in neurological diseases.

Convolution approach to evaluate amiodarone-HCl solid oral dosage forms

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Introduction: Amiodarone-HCl (AMD) is suggested for the treatment of life threatening ventricular and supraventricular arrhythmias as well as atrial fibrillation. To treat these diseases the tablet formulation is recommended. AMD is a compound with low solubility (0.35 mg/mL), high permeability, high protein binding (> 96%) and moderate bioavailability (35 – 65%). Food promotes drug absorption which improves bioavailability. AMD is classified by the Biopharmaceutic Classification System (BCS) as Class II drug and therefore, dissolution studies can be used to establish a meaningful in-vitro/in-vivo correlation through the prediction of drug plasma levels.

Purpose: To predict AMD plasma concentration-time profiles with in-vitro release data obtained with the USP paddle apparatus, dissolution media of physiological relevance and a convolution approach.

Method: AMD of reference and generic formulation were tested with USP paddle apparatus at 75 rpm and 900 mL of 0.1 N HCl (pH 1.2), pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. To promote the dissolution of the drug all dissolution media were added with 1% of sodium dodecyl sulfate (SDS). Automatic samples were withdrawn every 5 min over 60 min. Drug was spectrophotometrically quantified with the support of standard calibration curves in each pH at 243 nm. AMD dissolution profiles were compared with f₂ value. Suitable f₂ value is 50 – 100. Hypothetical AMD plasma levels were calculated with the methodology called convolution. The elimination rate, bioavailability factor, volume of distribution was used to build drug levels in function of time. Then, peak plasmatic level (C_{max}) and area under the plasma concentration-time profile from zero time to infinity (AUC_{0-inf}) were computed. AMD pharmacokinetic data of an in-vivo study were used to calculate the percent of Prediction Error (%PE) for C_{max} and AUC_{0-inf} (less than 10% is the optimal value).

Results: Despite addition of SDS in all dissolution media at 60 min less than 50% was released from both formulations at pH 6.8. The f₂ values at all pH's were more between 50 and 100 hence similar dissolution profiles were found. The PE values less than 10% for both pharmacokinetic parameters were found only for reference formulation at pH 4.5 acetate buffer + 1% SDS.

Conclusion: The best conditions to simulate AMD in-vivo behavior with data of reference formulation were USP paddle apparatus at 75 rpm and a volume of 900 mL of pH 4.5 acetate buffer + 1% SDS. These were the suitable conditions to predict AMD plasma concentrations similar to that found in an in-vivo study. The proposed predictions in the present work can be used as a support element to design better AMD solid oral dosage forms and the establishment of a meaningful in-vitro/in-vivo correlation.

Simulated in-vivo behavior of indomethacin capsules

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Introduction: Oral nonsteroidal anti-inflammatory drugs administered in high doses are suggested as first-line agents in the treatment of gout but may be contraindicated because of gastrointestinal hemorrhage or renal failure. Indomethacin is used for the treatment of rheumatoid arthritis and other chronic inflammatory diseases. This drug can cause severe gastrointestinal complications, increased blood pressure and decreased kidney function and the risk of developing these adverse effects increases in the case of high doses and prolonged treatments. Despite the documented adverse effects, indomethacin is widely prescribed and it is available as over-the-counter (OTC) formulations.

Purpose: To simulate the in-vivo behavior of indomethacin multi-source capsules with dissolution data and a convolution methodology.

Method: In-vitro release behavior of three multi-source formulations and the reference was determined with a USP basket apparatus at 100 rpm and 750 ml of pH 6.8 phosphate buffer as well as with the flow-through cell method with laminar flow at 16 mL/min. Indomethacin dissolution data were adjusted with First-order, Korsmeyer-Peppas, Makoid-Banakar, and Weibull model. The mathematical model that showed highest adjusted determination coefficient and lowest Akaike Information Criterion was selected as the best-fit model. Indomethacin plasma concentrations were predicted with a simple numerical convolution method. The in-vitro release data and published pharmacokinetic information were used to estimate the drug plasma concentrations. Hypothetical peak plasma level (C_{max}) and

area under the curve from zero time to infinity (AUC_{0-inf}) were computed and compared with those observed in an indomethacin bioavailability study. The predictability of the convolution analysis was established with the percent of prediction error (%PE) for both pharmacokinetic parameters. The optimal values should not exceed 10%.

Results: Similar dissolution profiles of two generic formulations in USP basket apparatus and only one generic formulation with the flow-through cell method were found ($f_2 > 50$). In all conditions, the in-vitro release performance fits to Weibull function since the established criteria were covered by this model. As the Weibull function better explains the release mechanism of all formulations in both USP dissolution apparatuses, dissolution profiles were compared with Td value. The Td data signifies the time interval necessary to release 63.2% of the drug contained in the dosage form. Statistically significant differences with all multi-source formulations, in both apparatuses, were found ($p < 0.05$). On the other hand, only PE $< 10\%$ for both pharmacokinetic parameters with dissolution data of reference drug product were found using the flow-through cell method. Same result was observed with only one generic formulation using the USP basket apparatus.

Conclusion: Because the PE results of reference formulation were within the established criteria (PE $< 10\%$ for C_{max} and AUC_{0-inf}) the flow-through cell method, laminar flow at 16 mL/min and pH 6.8 phosphate buffer were considered the most favorable conditions to test the multi-source formulations and predict their in-vivo behavior. This facilitates the evaluation of the biopharmaceutical quality of studied formulations. Therefore, these studies point to the flow-through cell method as the best tool to estimate the in-vivo indomethacin plasma levels of the used drug products.

Development of taste-masked orally dispersible tablets of metformin hydrochloride using spray drying and d-optimal design of experiments: Enhancing patient compliance

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Introduction: Diabetes mellitus type 2 (T2DM) is a chronic metabolic disorder that poses a significant global health challenge. Metformin hydrochloride (Met.HCl) is a primary treatment for managing T2DM. However, the current dosage form has low bioavailability and can be inconvenient for individuals with difficulty swallowing. This situation underscores the need for orally dispersible tablets (ODT) as

an alternative dosage form to enhance patient adherence and improve therapeutic outcomes. However, the formulation development is complicated by the low compressibility and strong bitterness of Met.HCl.

Method: This research utilizes a co-spray drying method to address challenges with Met.HCl by co-processing it with polyvinyl alcohol (PVA), mannitol, and sucralose, resulting in taste-masked spherical granules optimal for ODT formulation. The powder properties, solid-state characteristics, and bitterness of the co-processed Met.HCl, were evaluated. ODT formulations were designed with varying excipient ratios. Optimization was achieved using a D-optimal design of experiments (DOE) approach to obtain desired tablet properties, such as hardness and disintegration time.

Results: Spray drying enabled the homogenous distribution of excipients, lowered crystallinity, and improved the physicochemical characteristics of Met.HCl powder, overcoming the limitation of physical blending techniques. The co-spray dried powder showed enhanced flowability and compressibility, with angle of repose of 21.79° and a Carr's index of 29.71%. Scanning electron microscopy (SEM) validated the formation of spherical agglomerates with particle dimension D₅₀ 29.92 μm. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) solid-state characterization demonstrated a notable decrease in crystallinity, which improved compressibility and tabletability. The optimized formulation of Met.HCl ODT exhibited outstanding mechanical and functional characteristics, showcasing tensile strength between 1.90 and 2.43 MPa, fast disintegration times of 18 to 24 seconds, and total drug release within 5 minutes.

Conclusion: These results demonstrate the potential of spray drying as a particle engineering technique to enhance the physicochemical and functional properties of Met.HCl powder. This improvement supports the formulation of Met.HCl ODT offers a viable alternative for T2DM patients, particularly those with dysphagia. The ODT is designed to enhance Met.HCl bioavailability and accelerated onset time through pre-gastric absorption, compared to conventional tablets, which will be validated through ongoing in vivo pharmacokinetic studies. This study highlights the importance of innovative formulations in diabetes management and improving patient outcomes.

Amorphous solid dispersions of Felodipine with various molecular weights of PEG's for dissolution enhancement using organic solvent-free supercritical CO₂ processing: A green and sustainable technology

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Introduction: Solid dispersions (SDs) are one of the unique techniques used to improve the solubility. SDs contain at least two distinct components, usually a hydrophilic matrix and a hydrophobic drug. CO₂ exists as a critical fluid at critical temperature (T_c) 31.1°C and critical pressure (P_c) 7.38 MPa. This work aims to study the potential of scCO₂ as a processing medium to prepare SDs of Felodipine (FDP) in polyethylene glycols (PEG) varying different molecular weights at low temperatures and pressures without the use of organic solvent to enhance the dissolution profile of Felodipine and by using the best SDs to develop Felodipine orally disintegrating tablets (ODT) for the first time via supercritical carbon dioxide.

Method: The FDP-PEG SDs were prepared with 10%, 20%, and 30% w/w of FDP (Sigma) in PEG 4K, 6K, 10K, and 20K (Sigma). Polymer screening was performed, conducting phase monitor studies on Kollidon VA 64, Soluplus, Eudragit L100, and HPMC. Physical mixtures were prepared and carefully transferred into a clean and dry glass container and carefully placed in the high-pressure vessel (Thar Inc, USA) heated to 45 °C. The vessel was then filled with CO₂ (a liquid-CO₂ cylinder obtained from BOC Inc.) at a flow rate of 25 mL/min until 100 bar was achieved. The contents were continuously stirred (100 RPM) during the processing for 1 hour, the vessel was slowly depressurized at 20 bar/min. The obtained product was micronized by using a cutter mill (Retsch, Germany) assembled with 500 µm grater mesh. Best SD was selected to manufacture oral disintegrating tablets (ODT) using the Flexi Tab Tri Layer automated tablet compression machine (Roltgen marking systems).

Results: The solid dispersions of a drug (FDP) and polymer mixtures (PEG) were prepared successfully. The solid-liquid (S-L) transition of PEG 4000, 6000, and 10,000 showed at 40°C and 20000 showed at 50°C among the other polymers (Kollidon VA 64, Soluplus, Eudragit L100, HPMC). SDs prepared below the melting points of PEG 4K, 6K, and 10K at 45°C showed an amorphous nature confirmed by X-ray powder diffraction, and a diminished melting peak of FDP obtained from differential scanning calorimetry, while PEG 20K showed the best profile at processing temperature 60 °C. The scCO₂ process parameters, FDP-PEG ratios, and

molecular weight of PEG influenced the physicochemical properties of the drug, resulting in the amorphization improving the drug solubility.

Conclusion: In this study, a solvent-free scCO₂-based approach was utilized to develop solid dispersions of FDP that resulted in improved drug dissolution at all studied ratios. The scCO₂ process parameters, FDP-PEG ratios, and molecular weight of PEG influenced the physicochemical properties of the drug.

The ODT tablets were successfully developed using polyethylene glycol 4000 and 20,000 FDP-PEG 30% SDs that resulted in similar dissolution profiles to the SDs. ODTs manufactured with 4000 SD tablets failed the friability test (above 1%); tablets SD 20000 were good enough (friability 0.45%). Henceforth, FDP-PEG 20,000 was concluded as the best formulation for making ODT tablets with enhanced solubility without the use of organic solvents.

Fabrication of 3D-dimensionally printed chewable tablets for pediatrics using hot melt extrusion coupled with direct extrusion: A cutting-edge green and sustainable technology for continuous manufacturing

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Introduction: Chewable tablets are oral dosage forms intended to be chewed and then swallowed by the patient. This dosage form gained attention due to its ease of administration, making it suitable for pediatric patients. Lately, 3D printing has been investigated as an innovative technology for the production of personalized medicines. Within the current investigation, they described the fabrication of chewable tablets using hot melt extrusion and direct extrusion. This approach is advantageous as it avoids the printability issues of filaments, increases the bioavailability of compounds, and allows taste masking.

Method: Four different formulations of ibuprofen (Ibu), varying the qualitative and quantitative composition of the excipients Eudragit EPO Ready Mix, EPO, Galen IQ 981, Neusilin US2, Starch (F1), Xanthan gum (F2 & F3), Polyplasdone XL (F3), and croscarmellose sodium (CCS) (F4), were processed using a Rondol twin screw extruder at temperatures ranging from 70 to 90°C with a screw speed of

100 rpm and a feed rate of 150 g/hr. The extrudates were pelletized and directly fed into the 3D printer (80°C), which fabricated the chewable tablets in different shapes. The formulations were evaluated by XRPD, rheology, and a texture analysis. In addition, dissolution was performed using USP apparatus II at 37°C ± 0.5°C and 50 rpm speed. The tablets were assessed at pH 1.2 for 15 min, after which the pH was raised to 7.4 for the subsequent 45 min.

Results: Four formulations were successfully extruded via hot melt extruder. The pure Ibu is crystalline, while the diminished peaks in the formulation obtained from the XRPD diffractograms demonstrated amorphization essential in improving the solubility for the development of the chewable tablet. The Ibu-loaded pellets were conveyed to the printhead, which fabricated the Ibu chewable tablets. Formulations F1 and F2 were printable, although flow issues were observed; in addition, they failed to maintain their shape after printing, while F3 and F4 were able to maintain their structure and shape after printing, confirmed by the rheological studies and texture profiles. Among all the formulations, F4 showed better printability, as the cellulose derivative of CCS has the ability to maintain the viscosity of the formulation. In vitro dissolution studies of F4 showed a better dissolution profile in the presence of CCS compared with bulk Ibu and F3; xanthan gum in F3 delayed the drug release. Tablets were produced with different infill densities, which showed a significant impact on dissolution behavior.

Conclusion: The research project demonstrated the innovative integration of HME and direct extrusion for the continuous manufacturing of chewable tablets. This method addresses the printability challenges of filament-based techniques while improving solubility and taste masking. This technology also promotes real-time monitoring and analysis by integrating with Process Analytical Technology (PAT), scaling up, and essentially aiming to develop pharmaceutical dosage forms while being mindful of their ecological footprint. The novel approach can produce tailored pills at the point of care, with personalized, precise doses and promoting patient comfort and compliance.

Formulation and characterisation of paracetamol-loaded 3D tablets with co-processed excipients using selective laser sintering

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Introduction: The aim of this work was to investigate the possibility of 3D printing orally disintegrating tablets and prolonged release tablets formulated with StarLac® (85 %

(w/w) white native starch and 15 % (w/w) lactose monohydrate) and RetaLac® (50 % (w/w) lactose monohydrate and 50 % (w/w) hypromellose) as co-processed excipients and paracetamol as the active ingredient.

Methods: The dimensions, hardness, desintegration time, drug assay and dissolution studies of the obtained tablets were examined. Four different formulations were successfully printed using the selective laser sintering 3D printing technique. These formulations contained StarLac® and RetaLac® as diluents in varying amounts (66 %, 61 %, 56 % and 51 % w/w) and varying drug loadings (5 %, 10 %, 15 % and 20 % w/w), on a printing temperatures ranging from 85 oC to 100 oC (chamber temperature) and 95 oC to 110 oC (printing temperature) and laser scanning speed of 180 mm/s.

Results: Powder formulations with StarLac® exhibited good and passable flowability. Powder formulations with RetaLac® exhibited passable indirect flowability. All obtained tablets had cylindrical shape. Average mass (117.25 mg ± 7.92 to 192.66 mg ± 5.70), diameter (9.05 mm ± 0.68 to 9.59 mm ± 0.34) and thickness (3.32 mm ± 0.31 to 3.64 mm ± 0.29) of the tablets with StarLac® were smaller than tablets with RetaLac® (average mass from 130.77 mg ± 7.56 to 148.59 mg ± 5.97, average diameter from 9.26 mm ± 0.2 to 10.43 mm ± 0.21 and average thickness from 3.41 mm ± 0.2 to 3.89 mm ± 0.21). Average hardness of the tablets with StarLac® was greater (20.16 N ± 1.16 to 84.16 N ± 4.75) than tablets with RetaLac® (16 N ± 2.3 to 25.83 N ± 2.7). All the tablets with StarLac® disintegrated faster (18.33 s ± 1.53 to 33.33 s ± 2.08), than tablets with RetaLac® (1620.66 s ± 3.05 to 2036.33 s ± 4.04). The paracetamol content in each formulation ranged from 90.00 % (w/w) to 110.00 % (w/w), in accordance with the requirements set on in the European Pharmacopoeia. Tablets with StarLac® exhibited the characteristic dissolution profile of orally disintegrating tablets, with the total amount of paracetamol being released within 30 minutes. Tablets with RetaLac® exhibited characteristic dissolution profile of prolonged release tablets with the total amount of paracetamol being released after 250 minutes.

Conclusion: This results suggest that Selective laser sintering is a suitable technology for printing tablets that contain co-processed excipients with different release profiles of the active ingredient.

High-Strength gelatin hydrogel scaffold with roxadustat loading remodels the inflammatory microenvironment to enhance osteoporotic bone repair

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Introduction: Osteoporotic bone repair remains a significant challenge because of the imbalance between bone formation and resorption, primarily driven by the inflammatory microenvironment. Conventional anti-inflammatory therapies often fall short, as they not only exhibit limited efficacy but may also disrupt bone homeostasis, potentially exacerbating osteoporotic conditions. Hypoxia-inducible factor-1 α (HIF-1 α) represents a promising therapeutic target, due to its activation can mitigate inflammation and stimulate osteogenesis by enhancing osteoblast activity and differentiation. Capitalizing on this discovery, we developed a gelatin hydrogel scaffold optimized mechanical and biological properties, incorporating Roxadustat (an HIF-1 α stabilizer), to explore its potential and underlying mechanisms in remodeling the inflammatory microenvironment and enhancing osteoporotic bone regeneration.

Methods: The Roxadustat-loaded hydrogel scaffold was fabricated using methacrylated hyaluronic acid (HAMA), o-nitrobenzyl-modified gelatin (GelNB) and Roxadustat powder through a rapid crosslinking mechanism combined with digital light processing (DLP)-based 3D printing technology. The scaffold's mechanical properties, surface morphology, and drug release kinetics were analyzed via compression/tensile testing, scanning electron microscopy (SEM), and high-performance liquid chromatography (HPLC). Biodegradability was evaluated through enzymatic degradation assays. Biocompatibility was assessed using cell migration, adhesion, and rat subcutaneous implantation models. The scaffold's therapeutic ability in femoral defect repair was evaluated in osteoporotic rats through micro-CT imaging and histopathological analysis. Its modulation of the inflammatory microenvironment was assessed by Real-Time Quantitative Reverse Transcription PCR (qRT-PCR) and immunofluorescence staining. Furthermore, potential mechanisms of modulating inflammation were explored via RNA sequencing.

Results: In vitro studies demonstrated that the fabricated Roxadustat-loaded hydrogel scaffold exhibits excellent mechanical properties, biodegradability, biocompatibility, and controlled drug release kinetics. In vivo experiments revealed that the scaffold possesses significant osteoinductive and osteoconductive capabilities, promoting femoral defect repair in osteoporotic rat models at weeks 4 and 8 post-injury, with bone regeneration efficacy positively correlated with Roxadustat concentration. Compared to healthy rats, osteoporotic rats exhibited a more severe

inflammatory microenvironment on days 1, 4, 7, and 10 post-injury. The drug-loaded scaffold effectively suppressed inflammatory factor expression and immune cell infiltration in a precise and sustained manner, while increasing the M1/M2 macrophage ratio. Mechanistically, Roxadustat likely activates the HIF-1 α signaling pathway, inhibits the maturation and differentiation of myeloid dendritic cells (MDCs), and consequently regulates the inflammatory microenvironment.

Conclusion: In this study, we developed a gelatin hydrogel scaffold incorporating Roxadustat and demonstrated its ability to promote osteoporotic bone repair by modulating the early inflammatory microenvironment. Furthermore, we elucidated the underlying mechanism by which Roxadustat inhibits the mature differentiation of myeloid dendritic cells (MDCs) through activation of the HIF-1 α signaling pathway. Our research not only validates the therapeutic potential of inflammatory microenvironment remodeling for osteoporotic bone defects but also introduces a novel scaffold-and-Roxadustat combination therapy that specifically targets inflammatory microenvironments. This innovative approach offers an effective strategy for improving osteoporotic bone repair.

Fabrication and characterization of a novel drug delivery platform for metastatic triple negative breast cancer

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Introduction: Triple-negative breast cancer (TNBC) is an aggressive form of cancer, and there are yearly around 2500 new cases of TNBC in Australia. TNBC is not amenable to anti-hormone therapy or anti-HER2 targeted therapy, due to the lack expression of oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2). Chemotherapy is the most common treatment for TNBC. However, despite an initial response, many patients experience tumour relapse. Additionally, chemotherapy is associated with harmful side effects and is often ineffective in treating metastatic TNBC, highlighting the urgent need for more targeted and effective therapies. Moreover, TNBCs were found to be enriched in cancer stem cells (CSCs), which are relatively quiescent and intrinsically resistant to chemotherapy leading to the metastasis and relapses. It is, therefore, an urgent need to develop drug delivery systems that would specifically deliver the cytotoxic compound to the

tumour site and overcome chemotherapy resistance at the same time. Targeting luteinising-hormone releasing hormone receptor (LHRH-R) (expressed in 70-100% of TNBCs) is one approach by which targeted delivery of chemotherapy can be achieved. Combining the benefits of this approach with a CSCs inhibitor by conjugating both to a nanoparticle platform and using them as a combination is expected to improve the treatment efficacy and clinical outcomes of TNBC patients. Plasma polymerized nanoparticles (PPNs) are a new class of nanoparticles synthesized through plasma polymerization, allowing for a single-step functionalisation with molecular cargo without the need for linker intermediates. In this process, a plasma field is used to polymerize monomers, forming nanoscale particles with surface functionalities that enable direct cargo attachment.

Aim: The aim of this project is to optimize a method for the synthesis and characterization of PPNs conjugated to a novel CSC inhibitor (7C) and a previously developed novel LHRH-based peptide-drug conjugate (PDC) and evaluate the effectiveness of combining the developed conjugates.

Methodology: PPNs incorporating 7C and PDC have been characterised using High Performance Liquid Chromatography (HPLC), X-ray photoelectron spectroscopy (XPS), and dynamic light scattering (DLS). Biological studies including antiproliferative studies and colony formation assay were conducted.

Results: Functionalisation of the PPNs with the therapeutic molecules has been confirmed. The efficacy of the developed platforms has been proven in invitro biological studies.

Conclusion: the proven efficacy of the conjugated platform enhances their applicability for treating metastatic TNBC. However, it will be further evaluated via cell-based pharmacological studies including antiproliferation study and uptake in 3D culture.

Development of a Self-Emulsifying Drug Delivery System for Vitamin D3: A Novel Approach to Enhance Bioavailability

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Vitamin D is a vital fat-soluble vitamin that plays a key role in calcium homeostasis, bone health, and immune function. It is also linked to various chronic conditions, including diabetes, cardiovascular diseases, and autoimmune disorders. Despite

its importance, vitamin D deficiency remains a widespread health issue due to factors such as limited sun exposure, inadequate dietary intake, and the poor bioavailability of oral supplements. Since vitamin D's absorption in the gastrointestinal tract is highly dependent on its solubility in fat, enhancing its bioavailability remains a significant challenge.

This study focuses on improving the bioavailability and controlled release of vitamin D3 by utilizing self-emulsifying drug delivery systems (SEDDS) and solid self-emulsifying drug delivery systems (S-SEDDS). The goal is to develop lipid-based delivery systems that enhance the solubility and stability of vitamin D3, thereby improving its absorption and therapeutic effects. SEDDS is an advanced drug delivery technology consisting of oils, surfactants, and co-solvents, which spontaneously form oil-in-water microemulsions upon contact with an aqueous environment. These systems have demonstrated significant potential in enhancing the absorption of lipophilic compounds. Additionally, S-SEDDS, which involves converting liquid SEDDS into solid dosage forms, offers a promising strategy for ensuring both improved bioavailability and controlled drug release.

In vitro dissolution studies were carried out to assess drug release kinetics and evaluate the potential bioavailability enhancement achieved through SEDDS and S-SEDDS. The results indicated that the SEDDS formulations significantly improved the solubility and dissolution rate of vitamin D3 compared to conventional formulations. The developed systems exhibited high thermodynamic stability, low polydispersity index, and superior emulsification efficiency, demonstrating their potential for enhancing vitamin D3 bioavailability. Moreover, the S-SEDDS tablets exhibited uniform drug content, good flow properties, and desirable mechanical strength, making them suitable for oral dosage formulations. The dissolution studies further revealed that the S-SEDDS formulation facilitated a sustained release of vitamin D3, suggesting its potential for controlled drug delivery. These findings suggest that the developed systems could offer a more effective approach to vitamin D supplementation.

In conclusion, this study highlights the potential of SEDDS and S-SEDDS in improving the solubility, stability, and controlled release of vitamin D3. The preliminary results are promising, but further studies are necessary to confirm the clinical relevance and in vivo performance of these formulations. This research contributes to the growing field of lipid-based drug delivery and provides a foundation for future investigations into the clinical applications of these advanced delivery systems.

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Silica nanoparticle-based strategies to enhance atorvastatin: Improving solubility, bioavailability, and safety

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Introduction: Atorvastatin, a widely prescribed lipid-lowering drug, faces several challenges, including poor water solubility, low bioavailability, and rapid metabolism, which compromise its therapeutic efficacy. Nanotechnology offers a promising approach to improving the solubility and stability of atorvastatin, thereby enhancing its bioavailability, absorption, and therapeutic performance while potentially reducing the required dosage. This study aimed to develop a nanoparticle-based delivery system for atorvastatin to improve its solubility, stability, and sustained-release profile while minimising its adverse effects.

Method: Silica nanoparticles were synthesised using a nanoprecipitation-based method. The organic phase was prepared by co-condensing (3-mercaptopropyl) trimethoxysilane (MPTMS) and 3-aminopropyltrimethoxysilane (APTMS) at a fixed molar ratio under acidic conditions in the presence of a water-miscible solvent, such as dimethyl sulfoxide. After 24 hours, atorvastatin was incorporated into the organic phase. The resultant mixture was then injected into the aqueous phase and incubated in a circulating water bath at 60°C for two hours. The nanoparticles were subsequently collected and coated with bovine serum albumin (BSA). The BSA coating was employed to prevent particle aggregation and sedimentation while maintaining dispersion stability. Additionally, it enhanced hydrophilicity, facilitated drug loading and release, and thereby improved the overall performance of the nanoparticles. To evaluate the acute toxicity of orally administered SiNPs, we conducted histological examinations of major organs of rats 24 h after receiving low, medium and high doses compared to Lipitor®.

Results: The synthesised nanoparticles exhibits a spherical morphology, with an average particle size of 150.8 ± 28.4 nm and an average zeta potential of -18.9 ± 1.3 mV. The nanoformulation is generally biocompatible. The results do not reveal histological difference among the control group and the 3 treatment groups. The results are consistent with generally normal outcomes presented in biochemical and blood cell analysis

Conclusion: This study demonstrated the application of nanotechnology to enhance the solubility, bioavailability, and stability of atorvastatin. The BSA-coated nanoparticles

exhibited superior dispersion stability and drug loading efficiency. These findings underscore the potential of nanomedicine to overcome the limitations of conventional atorvastatin formulations, offering a more effective and safer drug delivery system with improved therapeutic efficacy.

Evaluation of rutin-pregabalin combination in the treatment of neuropathic pain induced by nerve injury

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Background: Neuropathic pain is a type of chronic pain resulting from a lesion or disease of the somatosensory nervous system's primary afferent neurons (Shinu et al., 2022). Medications used in the treatment of neuropathic pain often cause adverse effects. Additionally, since many patients suffering from this condition belong to the geriatric population, have polypharmacy issues, and present with comorbid diseases, these adverse effects can become more severe (Baron, 2009). Due to these challenges, neuropathic pain management is difficult, and in some cases, combination therapies may offer greater efficacy (Kerstman et al., 2013). Furthermore, plant-derived medications are considered alternative treatments and are widely used for various conditions such as pain and inflammation with minimal or no side effects (Hasnat et al., 2024).

Purpose: This study aims to evaluate the anti-allodynic effects of rutin at doses of 25, 50, and 100 mg/kg, both alone and in combination with 3 mg/kg pregabalin, in a chronic constriction injury (CCI)-induced neuropathic pain model in rats.

Material and Method: To induce neuropathic pain, the nerves of rats were ligated using the chronic constriction injury (CCI) model. Rutin was administered orally at the doses of 25, 50 and 100 mg/kg, both alone and in combination with pregabalin at 3 mg/kg at 30-180 min. time interval. Pain thresholds of the rats were assessed using the von Frey devices.

Results: The combination of 25 mg and 50 mg doses of rutin produced be the higher efficacy in the 60-120 min. interval compared to 30 mg pregabalin. The efficacy of all combination groups was found to be significantly greater at certain time intervals compared to the groups with only rutin or the 3 mg pregabalin group. It was observed that the antiallodynic effect of the combination of 25 mg rutin was significant in the 30-180 min interval compared to 3 mg

pregabalin, and the leading combination was the 25 mg group.

Discussion: This study demonstrated that the rutin-pregabalin combination holds potential for relieving neuropathic pain. The low-dose rutin-pregabalin combination, through their synergistic interaction, shortened the onset time of the antiallodynic effect, increased efficiency, and prolonged the duration of the effect.

Development of Curcumin-Loaded Buccal Films Using Deep Eutectic Solvents: An Innovative Strategy for Enhanced Solubility and Mucosal Delivery

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Background: Curcumin, a potent natural compound extracted from turmeric, exhibits significant therapeutic activities, including anti-inflammatory, antioxidant, and antimicrobial effects. Despite these beneficial properties, its clinical application is limited due to poor aqueous solubility and low bioavailability. Traditional formulations involving nanotechnology or lipid-based systems are complex and challenging for large-scale production. Recent advances suggest deep eutectic solvents (DES) significantly enhance drug solubility and bioavailability through simpler and scalable methods.

Purpose: This study aimed to develop optimized curcumin-loaded buccal films utilizing DES to overcome curcumin's inherent formulation challenges. The objective was to identify optimal parameters through experimental design, creating a practical, scalable, and effective formulation for localized oral mucosal treatment.

Method: A total of 14 DES formulations were prepared using combinations of hydrogen bond acceptors (choline chloride and betaine) with hydrogen bond donors (lactic acid and propylene glycol). The viscosity and pH of the DES systems and the solubility of curcumin were characterized, and the optimal DES system was selected based on the highest solubility enhancement. Curcumin solubility was evaluated via a validated high-performance liquid chromatography (HPLC) method. Buccal films were prepared using hydroxypropyl methylcellulose (HPMC K100) and Kollicoat® IR by solvent casting method. The design of experiments (DoE) was carried out using a Central Composite Design (CCD) with 20 experimental runs applied to optimize concentrations

of HPMC (X1), Kollicoat (X2), and DES (X3). Evaluated responses included film thickness, bioadhesive strength, elongation (%), swelling index (%), and swelling duration. The formulations optimized by DoE were characterized for mechanical properties, in vitro dissolution (USP Type V apparatus), ex vivo penetration on bovine buccal mucosa (Franz diffusion cells), and short-term stability assessment under controlled conditions.

Results: Curcumin's aqueous solubility, previously reported as approximately 0.6 µg/mL, was increased to 8.538 mg/mL in the optimal DES formulation, indicating an enhancement of over 10,000-fold. Formulations optimized through DoE demonstrated strong mechanical properties and bioadhesive performance and controlled swelling behavior. The thickness of the buccal films ranged between 0.4–0.8 mm, while bioadhesion, quantified as the work of adhesion, achieved a maximum value of 0.019 mJ/cm², confirming their strong suitability for buccal mucosal application. In vitro dissolution studies showed that curcumin release was completed within 12 hours, indicating a controlled release profile. Ex vivo permeation tests demonstrated efficient mucosal penetration.

Conclusion: This innovative study presents a highly promising and easily scalable approach for significantly enhancing the therapeutic effectiveness of curcumin through buccal film formulations employing DES. The simplicity, efficiency, and scalability of this approach represent a clear improvement over conventional complex formulations, offering improved patient adherence and therapeutic outcomes in oromucosal treatments.

The hidden benefits behind automating the comparative analysis of global proteomics datasets

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Introduction: Studying proteomics during drug delivery and new formulation research projects is becoming crucial as it plays a significant role in understanding biological systems and impacts pharmacokinetics. Many drugs act as substrates for membrane transport proteins or metabolising enzymes, impacting drugs' absorption, distribution, metabolism, and excretion (ADME). In addition, many small drug molecules and bio-therapeutics (such as monoclonal antibodies) act by maintaining protein function in cells. However, global

proteomics is a time-consuming quantitative analysis often limited to relatively highly expressed proteins. Moreover, when selecting a specific set of proteins to study, the analysis is done manually using Excel, making this process a laborious job prone to human errors.

Aim: To benchmark the “ADMExtract” R package, which automates proteomics analysis and facilitates proteomics studies for a non-proteomics expert within pharmaceutical research.

Method: Following a Bottom-Up approach to proteomics dataset analysis, protein assembly, peptide identification, and quantification were done using MaxQuant software. The ADMExtract tool on R used the outcome protein group file from MaxQuant to clean up the data and run statistical analysis.

Results: Five global proteomics datasets from various sources, including in-house and public repositories, were analysed using the pipeline established for this study. The ADMExtract tool quantifies and correlates ADME proteins using confirmed proteomics datasets derived from human tissues where the expression of ADME proteins in these organs is possible. Selecting a set of proteins using ADMExtract resulted in a quick and accurate analysis. The statistical analysis comparison was validated against the free software Perseus.

Conclusion: The ADMExtract tool is an open-source R-based package that provides an accurate and fast analysis of the global proteome for non-experts. It can be applied in pharmaceutical research for mining and quantitation, giving input parameters in downstream applications like physiologically based pharmacokinetic modelling (PBPK).

Evaluating the biological activities of novel nanoformulation for colorectal cancer treatment using optimised IncuCyte-based methodologies

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Introduction: Colorectal cancer (CRC) is the third most prevalent cancer globally, accounting for 10% of all cases and the second leading cause of cancer-related mortality, as reported by World Health Organisation. Conventional treatments such as chemotherapy, radiotherapy, and immunotherapy lack specificity, leading to toxicity in normal cells. Nanoformulations offer a promising alternative by improving drug targeting and reducing systemic side effects. The IncuCyte Live-Cell Analysis System plays a crucial role in

preclinical research, enabling real-time monitoring of cell proliferation, apoptosis, and migration. However, its application in nanoformulation evaluation remains limited due to the lack of standardised protocols for assessing nanoparticle-cell interactions. Establishing such methodologies could enhance its role in nanomedicine and improve the assessment of novel therapies.

Purpose: This study aims to develop a robust method for evaluating the cellular uptake and in vitro anti-proliferative activity of targeted and non-targeted curcumin-loaded nanoformulations for CRC. The non-targeted formulation consists of curcumin-loaded nanoparticles (Cur-NP), while the targeted formulations include curcumin nanoparticles conjugated with luteinizing hormone-releasing hormone (LHRH) derivatives 1 and 2 (Cur-NP-LHRH-D1 and Cur-NP-LHRH-D2). Using Caco-2 and HCT-116 cell lines, which overexpress LHRH receptors, this study assesses the targeting efficiency of these formulations.

Method: Live-cell imaging using IncuCyte® ZOOM was employed to quantify nanoformulation uptake by CRC cells over 48 hours. Masking fluorescence imaging was used to selectively analyse and quantify curcumin fluorescence, excluding background signals. To validate the performance of our optimised IncuCyte-based imaging method, standard methodologies including the MTT colorimetric assay, confocal microscopy, and immunohistochemistry (IHC) were used as reference techniques.

Results: LHRH receptor (LHRH-R) overexpression in Caco-2 and HCT-116 cells was confirmed via IHC, with Caco-2 exhibiting higher expression than HCT-116. Targeted nanoformulations showed greater curcumin uptake, validated by confocal IHC imaging, with a higher fluorescence confluence (5500 GCU × μm², 100 μM curcumin) than non-targeted formulations (4500 GCU × μm²) over 48 hours. At 2 hours, Caco-2 cells exhibited a higher fluorescence intensity (5000 GCU/μM) than HCT-116 (3000 GCU/μM), demonstrating LHRH-R-mediated targeting efficiency. The MTT assay further confirmed greater cytotoxicity of the targeted nanoformulation, showing a more rapid decline in cell viability at lower drug concentrations, reinforcing improved therapeutic efficacy through LHRH-targeted delivery.

Conclusion: LHRH-targeted nanoformulations demonstrated enhanced curcumin uptake and greater cytotoxicity in colorectal cancer cells, correlating with LHRH receptor expression levels. Using MTT and IHC as standard methodologies, a direct correlation between their results and our optimized IncuCyte-based method confirmed IncuCyte’s feasibility for assessing nanoformulation uptake and therapeutic efficacy. This validation supports IncuCyte as a reliable tool for real-time targeted drug delivery evaluation in CRC treatment.

Dissolvable microneedles loaded with caffeine and adenosine for the treatment of Androgenetic Alopecia

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Introduction: Androgenetic alopecia (AGA), or male pattern baldness, is a common condition caused by hormonal and genetic factors, mainly due to the effects of dihydrotestosterone (DHT) on hair follicles. Traditional treatments like minoxidil and finasteride can be effective but have side effects and inconsistent results. Alternative therapies, including bioactive compounds like caffeine and adenosine, show promise in promoting hair growth. Microneedling, which enhances drug absorption, has emerged as a potential method to improve treatment outcomes. This study investigated the use of microneedles containing caffeine and adenosine as a novel, effective approach to treat AGA.

Methods: Microneedle arrays were fabricated using a molding technique with polydimethylsiloxane (PDMS) molds to achieve optimal size, shape, and precise control over the release of hair growth-promoting compounds. These molds were then utilized in the final stage to create polymer-based microneedles. The microneedles were composed of a polymer blend of polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP) in a 1:10 ratio, dissolved in water. Biocompatible polymers were selected to incorporate caffeine and adenosine into the microneedles, ensuring both safety and efficacy. This formulation was specifically designed for the controlled release of active compounds, facilitating deep penetration into the scalp to enhance therapeutic effects. The drug loading of the microneedles was assessed using phosphate-buffered saline (PBS) and high-performance liquid chromatography (HPLC) analysis. Drug release was evaluated both in PBS medium and through rat cadaver skin using a Franz diffusion cell.

Results: A 20×20 array of microneedles (400 small needles) was fabricated, with drugs incorporated into the dissolvable polymer matrix. The drug load for this array, quantified using high-performance liquid chromatography (HPLC), was 186 µg for caffeine and 643 µg for adenosine.

Conclusions: Microneedles loaded with hair growth-promoting compounds, such as caffeine and adenosine, present a promising and minimally invasive approach to combat male pattern hair loss. These microneedles can efficiently deliver active ingredients directly to the scalp, bypassing the stratum corneum and enabling deeper penetration into the hair follicles. This targeted delivery not only enhances the efficacy of the compounds but also

reduces the potential side effects often associated with oral treatments. By promoting hair growth and preventing further hair loss, this innovative technology offers a safe, convenient, and effective solution for individuals seeking to manage or reverse the progression of male pattern baldness.

Targeting the TSP1/ TXR1 axis with metronomic micellar docetaxel to overcome chemoresistance in triple-negative breast cancer

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Introduction: Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer with limited treatment options, primarily relying on chemotherapy. Docetaxel (DTX) is a key chemotherapeutic agent for TNBC; however, its clinical efficacy is often hindered by drug resistance, poor solubility, and high-dose-related toxicity. Metronomic chemotherapy (MCT), which involves low-dose, frequent drug administration, has emerged as a promising strategy to enhance chemosensitivity while minimizing adverse effects. However, the underlying mechanisms by which MCT improves TNBC response to DTX remain unclear. This study aims to elucidate the role of thrombospondin-1 (TSP1) in mediating the chemosensitizing effects of MCT with DTX in TNBC and to develop a targeted nanodelivery system to enhance therapeutic efficacy and reduce systemic toxicity.

Method: Transcriptomic analysis was performed to explore the molecular mechanisms of MCT-induced chemosensitivity in TNBC. Human umbilical vein endothelial cells (HUVECs) were used to investigate TSP1 secretion upon MCT treatment. Functional assays were conducted to assess the impact of TSP1 on early growth response protein 1 (EGR1) and TXR1, a gene associated with taxane resistance. To improve drug delivery efficiency, DTX was encapsulated into micelles (DTX-NP-cRGDfk) conjugated with the cyclic RGDfk peptide for targeted tumor and vascular delivery. The therapeutic efficacy of this formulation was evaluated in vitro and in vivo.

Results: MCT with DTX significantly upregulated TSP1 secretion from HUVECs, enhancing TNBC chemosensitivity by destabilizing EGR1 and downregulating TXR1 expression. The targeted micellar DTX formulation (DTX-NP-cRGDfk) achieved efficient tumor accumulation, further amplified TSP1 secretion, and exhibited potent anti-tumor effects, promoting apoptosis in TNBC cells. In vivo studies confirmed that this approach improved therapeutic outcomes compared to conventional DTX treatment.

Conclusion: This study reveals a novel mechanism by which MCT enhances TNBC response to DTX through TSP1-mediated regulation of chemoresistance pathways. Additionally, targeted micellar delivery of DTX optimizes treatment efficacy while reducing systemic toxicity. These findings support the potential of combining MCT with nanotechnology-based drug delivery systems as an effective therapeutic strategy for TNBC.

Synthesis and characterization of surface modified and stimuli responsive mesoporous silica nanoparticles loaded with Epigallocatechin Gallate (EGCG) for drug delivery applications

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Nanotechnology has offered a more reliable alternative to achieving better treatment outcomes in disease management and diagnosis through the use of multifunctional biocompatible nanomaterials. For drug delivery purposes, the most widely studied nanomaterial is mesoporous silica nanoparticles (MSNs) which have been explored as an effective delivery system for small molecule chemotherapeutic agents due to their high stability in physiological media, biocompatibility, and their unique ability to encapsulate large amounts of cargo molecules and deliver same to the targeted site. The study herein evaluates the effect of surface modification on the functionality of MSNs synthesized by a sol-gel process involving the use of n-Cetyl trimethyl-ammonium bromide (CTAB) as the surfactant template and tetraethyl orthosilicate (TEOS) as the silicon source. Functionalization of the mesoporous nano-based material was achieved by co-condensation of (3-aminopropyl) triethoxysilane (APTES) giving rise to amino-functionalized MSNs (MSN_{NH2}). Using epigallocatechin gallate (EGCG) as the cargo molecule, the physicochemical properties of the synthesized nanoparticles were carefully investigated. Results obtained showed a notable enhancement of the encapsulation efficiency, loading capacity, release behavior, and pH sensitivity of amino-functionalized MSNs compared to the non-functionalized MSN. The results of this study validates the benefits of amino functionalization in improving the functional characteristics of MSN.

Evaluating the efficacy of valproic acid-loaded lipid nanoparticles for nose-to-brain delivery using a 3D-printed nasal cast

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Introduction: Nose-to-brain (N2B) transport primarily occurs in the olfactory region, where drugs can reach the brain directly via the olfactory nerves. Therefore, maximizing olfactory deposition (OD) is crucial for effective N2B delivery. In this study, we evaluated the effectiveness of valproic acid-loaded nanostructured lipid carriers (VPA-loaded NLC) for N2B transport.

Methods: For the experiments, an optimised aqueous dispersion of VPA-loaded NLC was placed in three different delivery devices supplied by Aptar Pharma (VP7 232 N2B, UDS1 and Preloaded). Their ability to maximise OD was assessed after actuation of each device in a 3D-printed nasal cast (Aeronose®). In addition, the influence of positional variation on OD was evaluated to determine the most suitable device for effective N2B delivery.

Results: The highest OD was achieved with the Preloaded device (43.33 ± 4.73%), followed by VP7 (39.90 ± 6.27%) and UDS1 (18.10 ± 3.87%). The most significant positioning variable was the angle relative to the horizontal plane (A1). An A1 of 53° maximized OD for both the Preloaded and VP7 devices, while 30° was optimal for UDS1. Additionally, a lateral angle of 5° resulted in higher OD compared to 10°, and deeper insertion further enhanced OD.

Conclusion: This study concluded that both the choice of delivery device and its positioning play a crucial role in OD, providing valuable insights for the design of nasal devices intended for the N2B route.

Bioinspired hydrogel without hormones for female-controlled on-demand prevention of unintended pregnancy

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Introduction: The high incidence of unintended pregnancies across the globe suggests that current contraceptive methods do not deliver the desired impact and/or gender norms limit women's ability to access/use existing preventive tools. Therefore, the challenge of the future is to develop innovative, women-controlled contraceptive technologies that are affordable and socially acceptable. The main objective of this research is to develop a low-cost, female-controlled on-demand product that augments the natural contraceptive properties of the female reproductive tract without the use of hormones.

Methods: A hydrogel comprised of equivalent amounts of Carbopol® 974P (CP) and polyvinylpyrrolidone (PVP) was fabricated using conventional sol-to-gel transformation. Viscoelastic gel properties in the presence and absence of vaginal fluid simulant, pH 4.2 (VFS), and/or seminal fluid simulant, pH 7.7 (SFS) were quantified using the TA-XTPlus Texture Analyzer. In parallel, buffer capacity of the gel phase was measured using a DeltaTrak® ISFET pH probe. Migration rate and motility of human sperm before and after interaction with the CP/PVP hydrogel were quantified microscopically to assess contraceptive efficacy *in vitro*. Experiments were performed at least in triplicate. A statistically significant difference ($p < 0.05$) between treatment groups was assessed utilizing one-way analysis of variance or two-sided Student's *t* test for pairwise comparison.

Results: Viscoelastic gel properties significantly increased upon exposure of the CP/PVP hydrogel to alkaline SFS, resulting in a 118% greater work of shear measured at a volumetric gel/fluid ratio of 1:1 (5.80 ± 0.10 Nxs vs. 2.66 ± 0.01 Nxs for gel only). Further addition of SFS appeared to dilute the gel structure, which was quantified by continuous reduction in the work of shear from 5.80 ± 0.10 Nxs to 3.85 ± 0.21 Nxs at a volumetric gel/fluid ratio of 1:4. The pH value of the gel phase measured under those conditions increased from pH 3.40 to 4.95. In comparison to the marketed acid-buffering Phexxi® gel, the number of human sperm capable of traversing a CP/PVP gel barrier was reduced by 90%. More importantly, motility of sperm cells that were able to overcome the CP/PVP gel barrier was <10%.

Conclusion: The bioinspired CP/PVP hydrogel demonstrates bioresponsive physicochemical properties after exposure to alkaline seminal fluid that severely restrict sperm movement *in vitro*. These promising results support further evaluation of this innovative bioengineering concept as a drug-free,

female-controlled on-demand contraceptive using preclinical animal models.

AI-driven 3D drug printing: A new frontier in precision medicine and patient-centric drug development

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Introduction: The integration of artificial intelligence with three-dimensional (3D) drug printing promises to transform personalized medicine with unprecedented accuracy. Though 3D printing allows for customized drug formulations, AI's potential can optimize these processes in real-time, using patient-specific data to improve therapeutic outcomes. However, the role of AI in automating and optimizing patient-centered pharmaceutical manufacturing still underdeveloped.

Purpose: This research explores how AI-driven algorithms and 3D drug printing may revolutionize drug personalization by optimizing dosage, release kinetics, and formulation based on real-time physiological, genetic, and disease progression data.

Methods: A comprehensive review of recent advancements in AI-driven 3D drug printing, focusing on clinical applications, quality assurance, and regulatory considerations was conducted using a systematic search from 2018 to 2025. Thematic synthesis was used to categorize the AI applications into key areas, identifying advancements, challenges, and regulatory gaps in implementing AI-assisted 3D drug printing for patient-centric medicine.

Results: AI-driven drug printing systems can use machine learning to calibrate doses automatically, detect anomalies in the printing process, and predict patient treatment success. Machine learning and predictive modelling technologies allow 3D-printed medications to change dynamically in response to a patient's unique circumstances. Machine learning models analyse pharmacokinetic statistics before printing, suggesting an optimal formulation, cutting out the need for trial-and-error adjustments. Furthermore, AI-powered sensors in printing systems can ensure in-process quality control. Even with these benefits, challenges remain in regulatory approval, data security, and ethical considerations.

Conclusion: AI and 3D drug printing represent a paradigm shift in drug manufacturing, enabling a truly adaptive patient-centered approach. Further research is needed on AI-based quality assurance protocols, ethical guidelines for real-time personalized drug synthesis, and regulatory frameworks. Pairing a patient-centered printing style with AI-driven

automation provides an unseen level of safety and therapeutic effectiveness.

A sustainable sensor for hydroxychloroquine purity assessment: A quality-by-design approach

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Introduction: Hydroxychloroquine (HCQ) is a widely used drug for autoimmune diseases and malaria, with significant industrial and clinical relevance. However, its synthesis process introduces toxic impurities, including 4,7-dichloroquinoline and hydroxynovoldiamine, necessitating a rapid and selective purity assessment method. Conventional chromatographic techniques, while effective, are resource-intensive and less adaptable for real-time monitoring.

Purpose: This study aims to develop and optimize a selective, eco-friendly, and cost-effective potentiometric sensor for the real-time determination of HCQ purity in pharmaceutical manufacturing, ensuring accurate detection of key synthesis impurities.

Method: A customised Quality-by-Design (QbD) approach was used to systematically optimize the sensor's membrane composition using various ion exchangers (tetraphenylborate, phosphotungstate), plasticizers (dibutyl phthalate, nitrophenyl octyl ether), and ionophores (β -cyclodextrin, calix [8] arene). Various sensor formulations were formulated, tested, and their electrochemical responses were evaluated. Molecular docking simulations further interpreted the interaction mechanisms between HCQ and the selected ionophores to confirm the interaction efficiency of the optimized ionophore.

Results: The optimized sensor demonstrated a near-Nernstian response with excellent linearity, with a correlation coefficient < 0.990 and a rapid response time about 6 seconds. It demonstrated high selectivity for HCQ over 4,7-dichloroquinoline and hydroxynovoldiamine, ensuring accurate detection in presence of impurities. The working pH range of 2.0–8.0 guaranteed the broad applicability of the suggested method in different sample matrices. Molecular docking confirmed a strong host-guest interaction between HCQ and β -cyclodextrin that improves the sensor performance.

Conclusion: The developed sensor provides a rapid, sensitive, and sustainable solution for HCQ purity assessment. The method offers a real-time detection alternative to previously reported traditional methods. Its portability, cost-effectiveness, and alignment with green chemistry principles make it an ideal tool for pharmaceutical quality control, ensuring efficient and eco-friendly drug manufacturing processes.

ChemoGell - a thermosensitive injectable drug delivery vehicle for direct intratumoural delivery

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Introduction: Treatment for cancer is traditionally based around the three pillars of surgery, chemotherapy and radiation with immunotherapies playing an increasingly important role in certain cancers. Standard drug regimens are primarily delivered to the patient via intravenous (IV) injection, with the concomitant off-target toxic side effects leading to significant patient morbidity due to lack of specificity of treatment.

For certain clinical indications intratumoural delivery (IT) provides potential benefits to treatment including minimally invasive administration, localisation of chemical payload at tumor site and subsequent reduction in off-target side effects, however retention and local toxicity can present challenges.

ChemoGell™ is a novel patented thermosensitive injectable polymer drug delivery system intended for IT delivery, currently being developed through a spin-out company OncoLize. It is liquid and injectable at room temperature but transitions to a semi-solid drug depot at physiological temperatures. It can be loaded with a range of chemotherapeutics enabling improved delivery and retention at the tumour site, and prolonged duration of release and activity of drug. Its first line clinical indication is pancreatic adenocarcinoma (PDAC).

Methods: Gemcitabine loaded ChemoGell™ (ChemGem™) was formulated and characterised for material properties including sol-gel transition temperature, release, injectability, disintegration, stability and lyophilisation. The final product was a lyophilised foam like wafer that could be reconstituted to form a gemcitabine loaded thermosensitive polymer solution. This formulation was evaluated in a patient derived xenograft (PDX) model of PDAC using an immunodeficient mouse model. Mice received a subcutaneous implant of an

established PDAC PDX in the right flank and were treated once tumours reached a predetermined size. Mice were divided into 3 groups (ChemoGell™, ChemGem™ and saline) and 2 injections were performed at day 0 and day 8. Upon reaching the humane endpoint or max. 112 days post inoculation, mice were euthanized. Molecular characteristics of these end stage tumors were further investigated by hematoxylin and eosin (HE) and immunohistochemical (IHC) stainings using pan-cytokeratin, vimentin, Ki67 and CC3 antibodies.

Results: The ChemGem™ formulation was shown to have suitable material properties for in vivo evaluation, including appropriate sol-gel transition temperatures, gemcitabine release and injectability through clinically relevant needles. Lyophilisation was an effective method for enhancing stability with freeze-dried product stable for upto at least 3m, and reconstitution by the drug solution feasible. In vivo evaluation in a PDX PDAC mouse model showed tumor growth rate was significantly reduced in ChemGem™ treated mice, compared to exponential growth in saline, and slightly later, in ChemoGell™ treated mice. No significant changes in weight were identified. None of the CG-Gem treated mice reached the experimental endpoint and all were alive at the end of experiment. In contrast, all blank CG and saline treated mice tumour volumes did, with a median survival of 45 days and 25 days, respectively. Reductions in pan-cytokeratin and increases in vimentin expression were confirmed in CG and CG-Gem compared to saline treated tumors. Overall ChemGem™ induced significantly improved mouse survival (100%) and reduced tumour growth. ChemGem™ is currently being progressed through nonclinical testing with a view to First-in-Human clinical trials.

Preparation and evaluation of novel ascorbic acid-based thin film for nicotine cessation and cotinine detoxification

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Introduction: Tobacco use remains a major global health challenge, contributing to approximately six million deaths annually and imposing significant social, economic, and environmental burdens, particularly in developing nations. Nicotine, the primary psychoactive compound in tobacco, is responsible for addiction. It is metabolized into cotinine, an oxidative metabolite that persists in the body for several weeks and contributes to toxicity. Conventional nicotine replacement therapies (NRTs) introduce additional nicotine into the body, sustaining addiction and leading to increased cotinine accumulation. Addressing both nicotine dependence and cotinine toxicity requires an alternative approach. Based on our earlier clinical findings demonstrating that ascorbic

acid (vitamin C) effectively converts cotinine back to nicotine in human plasma, we developed a novel fast-dispersing thin film incorporating ascorbic acid as a therapeutic intervention for smoking cessation.

Methodology: A novel fast-dispersing thin film containing ascorbic acid was formulated using a biodegradable polymer, and its release and disintegration characteristics were analyzed. The release pattern of ascorbic acid was evaluated through an in-vitro release study in artificial saliva. The film was placed in 4 mL of artificial saliva and subjected to agitation at 55 rpm. Samples were collected at 0.5, 1, 3, 5, 7, 9, 11, 13, and 15 minutes, and ascorbic acid concentrations were quantified using high-performance liquid chromatography (HPLC). Additionally, a disintegration test was conducted using a USP disintegration apparatus with artificial saliva as the medium. The bath temperature was maintained at 37°C, and the films were placed in the medium. The system was programmed to maintain this temperature, after which the films were loaded into test tubes with a disc placed over them to prevent floating. The apparatus was then run until complete disintegration of the film was observed, and the time was recorded.

Results: The formulated thin film incorporating ascorbic acid dissolved within 33 seconds in artificial saliva, achieving an 80% release in the in-vitro study. The release profile demonstrated a sustained and controlled dissolution of ascorbic acid, ensuring optimal bioavailability. The disintegration test confirmed rapid breakdown of the film within the physiological conditions of the oral cavity, further supporting its effectiveness as an oral nicotine cessation aid.

Conclusion: This study highlights the successful formulation of an ascorbic acid-based thin film designed for nicotine cessation and cotinine detoxification. The rapid disintegration and high release efficiency emphasize its potential as a promising intervention for tobacco cessation. With encouraging preclinical findings, the thin film formulation is progressing towards clinical trials, supported by industrial collaboration. Further studies are in progress to evaluate its efficacy in a real-world smoking cessation program. This innovative approach, protected by a national patent with an international patent in progress, holds significant potential for transforming nicotine addiction treatment strategies.

Hypothetical ketoprofen plasma concentrations from dissolution data of multi-source capsules and a convolution approach

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Introduction: Ketoprofen is a nonsteroidal anti-inflammatory drug used as antipyretic, analgesic, and anti-inflammatory in the treatment of rheumatoid arthritis and osteoarthritis. Ketoprofen is known for its negative gastrointestinal effects and low plasma half-life. It is a Biopharmaceutics Classification System class II drug. Poorly water-soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability. For a poorly soluble drug, the influence of solubility and dissolution rate is more significant, since for orally administered drug, it is a prerequisite to be dissolved in the digestive fluid to ensure the absorption of the administered dose through the bio-membrane of the alimentary tract.

Purpose: To propose hypothetical ketoprofen plasma levels with dissolution data of multi-source formulations and a convolution approach.

Method: Dissolution profiles were determined with an USP apparatus type II at 50 rpm. Ketoprofen dissolved was determined with standard calibration curves at 260 nm. Capsules were sprinkled on 900 ml of phosphate buffer (pH 7.5). Dissolution profiles were also obtained with an USP Apparatus type IV with 22.6-mm cells. Laminar flow was used. The dissolution media phosphate buffer (pH 7.5) was pumped at 16 ml/min. Dissolution data were adjusted to Gompertz, Makoid-Banakar, Peppas-Sahlin, and Weibull model. The model with the highest adjusted determination coefficient ($R^2_{adjusted}$) and minimum Akaike Information Criterion (AIC) was selected as the best-fit model. Ketoprofen plasma concentrations were simulated through the Inverse Release Function approach. This methodology allows an adjustment in the time scale of the dissolution profile to facilitate the establishment of a meaningful in-vitro/in-vivo correlation. When the new time scale of the dissolution profile was calculated, predicted ketoprofen plasma concentrations in function of time were estimated with a simple numerical convolution method.

Results: Due to dissolved drug from reference formulation in USP apparatus type II was more than 90% at 10 min no f_2 similarity factors for multi-source drug products were calculated. With dissolution data from USP apparatus type IV all f_2 values were less than 50. Then, dissolution profiles of multi-source formulations were not similar to dissolution profile of reference drug product. It is observed that the drug release fits different models since the previously established $R^2_{adjusted}$ and AIC criteria are covered by different

equations. As the equation describing in-vitro drug release in the reference formulation differs from the equations for multi-source formulations, the dissolution profiles were not compared with this approach. With the USP apparatus type II, C formulation showed PE values <10% for both pharmacokinetic parameters, while with the USP Apparatus type IV only reference drug product showed C_{max} and AUC_{0-inf} values less than 10%.

Conclusion: Hypothetical in-vivo performance of ketoprofen from multi-source formulations was determined with in-vitro release data from USP apparatus type II and IV and better results for reference formulation were observed with the USP apparatus type IV. For its hydrodynamic characteristics that are like those found in the gastrointestinal tract the flow-through cell method is the best option to predict in-vivo performance of ketoprofen multi-source formulations.

Prediction of ibuprofen plasma levels from in-vitro release data of suspensions

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Introduction: The in-vitro release experiments with the standard paddle apparatus involve large volumes of test media hence to study small samples it would be desirable requires smaller volumes of media but with same reliability as the standard USP apparatus. Different types of mini-paddle apparatus show a miniaturized reproduction of the paddle method. Due to the possibility of working with smaller samples and volumes, the mini-paddle apparatus offers advantages in terms of substance, analytical, and material cost saving when evaluating release mechanisms. On the other hand, it is known that the flow-through cell method better simulates the gastrointestinal tract. It has a nonstop extraction of the drug, producing an intermittent flow into the place where the formulation is positioned. This apparatus is suitable to study poor-water soluble drugs as ibuprofen.

Purpose: To propose plasma concentration-time profiles of ibuprofen pediatric suspensions with in-vitro release data of the mini-paddle apparatus and the flow-through cell method.

Method: Dissolution profiles of ibuprofen were obtained using the mini-paddle method at 75 rpm and 200 ml of dissolution medium. The flow-through cell method with laminar flow at 16 ml/min was operated. Dissolution medium was phosphate buffer (pH 6.8). A suspension sample containing 10 mg of ibuprofen was tested. 5 ml of dissolution samples were taken at 10-, 20-, 30-, 45-, and 60-min. To quantify ibuprofen a derivative spectrophotometric method was used. Dissolution profiles of four ibuprofen multi-source suspensions vs. reference were related with different

approaches. The f_2 similarity factor, dissolution efficiency (DE) and mean dissolution time (MDT) were computed. If $f_2 = 50 - 100$ similar profiles were considered. Comparisons of DE and MDT were carried out with a one-way ANOVA and a post hoc Dunnett's multiple comparisons test. If $p < 0.05$ statistically significant differences were considered. The hypothetical in-vivo behavior was simulated with a numerical convolution approach. After calculation of ibuprofen plasma concentration-time profiles the peak plasma level (C_{max}) and area under the concentration-time curve from zero time to infinity (AUC_{0-inf}) were calculated. An ibuprofen bioavailability study was used to compare predicted pharmacokinetic parameters. The computation of prediction error (%PE) for C_{max} and AUC_{0-inf} was carried out and PE values less than 10% were considered as optimal.

Results: Similar dissolution profiles with one generic formulation using the mini-the paddle method and all multi-source formulations with the flow-through cell were found ($f_2 > 50$). Statistically significant differences were found in some model-independent parameters using both dissolution methods ($p < 0.05$). PE $< 10\%$ for both pharmacokinetic parameters of reference formulation and two multi-source products were found with the flow-through cell method.

Conclusion: The flow-through cell method at 16 ml/min and phosphate buffer (pH 6.8) were the suitable settings to evaluate ibuprofen multi-source drug products since these dissolution conditions were able to generate, with reference formulation, an in-vivo behavior similar to that found in a bioavailability study. By the obtained findings the use of the flow-through cell method is suggested to test ibuprofen pediatric dosage forms. To corroborate results, human studies with the used formulations are necessary.

Process development of non-ionizing, microbial remediation for medicinal cannabis flower

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Introduction: The compact morphology and dense flower structure of cannabis make it more susceptible to microbial contamination, increasing the difficulty of microbiological control during cultivation and production. Microbial contamination can lead to product losses and pose health risks, particularly to immunocompromised patients. While ionizing irradiation is commonly used, non-irradiated product is preferred in Germany. Advanced oxidation technologies, generating short-lived oxidative free radicals, can reduce microbial levels by disrupting microbial cell integrity.

Method: The design of a non-ionizing microbial remediation process was evaluated using the following methodology:

Phase I – Product Planning

Focus group discussions and Quality Function Deployment (QFD) were employed to define the product plan. A House of Quality (HoQ) matrix integrated competitor analysis, regulatory requirements, and desired characteristics to establish functional requirements.

Phase II – Product Design

A second HoQ matrix translated technical and quality requirements into engineering characteristics, leading to the selection of a closed-system setup with cold plasma ozone generation. Critical process parts were classified using Failure Mode and Effects Analysis (FMEA), and suitable specifications were proposed.

Phase III – Process Development and Validation

Critical Quality Attributes (CQAs) were identified based on the Ph. Eur. 3028 cannabis monograph, classified by criticality, and assessed through FMEA to identify variables impacting CQAs. Critical Process Parameters (CPPs) were established, and a validation protocol was formulated in line with Eudralex Volume 4 Annex 15 requirements.

Results: The study identified key quality characteristics for a non-ionizing cold plasma ozone system. HoQ matrix weighting indicated higher priority for certifiable design (EU-GMP/CE), selective microbial reduction, and optimal cycle parameters. A correlation matrix favored an ozone closed system due to positive trade-offs. Design features included modular construction, ozone-resistant materials, and automated controls. Risk assessment identified issues like ozone leakage and pressure build-up, which were mitigated through improved seals, exhaust systems, and programmable safety controls. Critical components such as SS316L chambers, ozone sensors, and generators were evaluated for process reliability. A control strategy was established to manage CQAs and process parameters. Ozone concentration and cycle time directly affected microbial remediation efficacy, with lower ozone and shorter cycles reducing effectiveness, while higher levels increased byproducts and altered the product's composition. A process development method and validation protocol were proposed to optimize process parameters.

Conclusion: Limited research exists on non-ionizing microbial remediation of medicinal cannabis. This study integrates engineering and regulatory considerations to develop a scalable, EU-GMP-compliant system, addressing critical design aspects such as material compatibility, process control, and risk mitigation. Focus group discussions, Quality Function Deployment (QFD) and failure modes effect analysis methodologies, were successfully integrated to conduct product planning and design. The proposed process aims to reduce microbial content to acceptable levels rather than achieve full decontamination, providing an additional control measure to lower bioburden and enhance patient safety without significantly altering product quality. Further practical and validation studies are required to refine and optimize the process, with the aim of developing a commercially viable microbial remediation solution for the

pharmaceutical cannabis industry, and potentially for other sectors requiring microbial control.

Tumor microenvironment-activatable copper MOF Nanoplatfom triggers synergistic cuproptosis/ferroptosis via fenton catalysis for enhanced antitumor therapy

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Background: Cancer remains one of the most challenging diseases, characterized by its high incidence and mortality rates worldwide. Conventional therapeutic modalities—surgery, chemotherapy, and radiotherapy—are often limited by severe adverse effects, prolonged treatment durations, and elevated recurrence rates. These limitations underscore the urgent need for innovative therapeutic strategies that can selectively target cancer cells while minimizing damage to healthy tissues.

Aims: To develop a novel, efficient, safe, and low-toxicity therapeutic strategy that synergizes chemodynamic therapy (CDT) and cuproptosis by exploiting the unique biochemical features of the tumor microenvironment (TME). The goal is to create a precision cancer therapy that leverages the TME's distinct characteristics to enhance therapeutic efficacy and reduce systemic toxicity.

Methods: A novel nanosystem, Cu-TCPP-MnPC, was engineered by integrating a two-dimensional copper-based metal-organic framework (MOF) composed of Cu-TCPP (a copper-porphyrin complex) with a manganese porphyrin coordination compound (MnPC). This design capitalizes on the TME's acidic pH and altered redox state for targeted activation. The nanosystem was characterized using advanced spectroscopic and microscopic techniques to confirm its structural integrity and functional properties. In vitro and in vivo experiments were conducted to evaluate its therapeutic efficacy and safety.

Results: Under the slightly acidic conditions of the TME, TCPP-Cu-MnPC releases Cu²⁺ ions and the manganese complex. The released Cu²⁺ ions participate in Fenton-like reactions, generating cytotoxic reactive oxygen species (ROS) that induce oxidative stress and damage cancer cells. Simultaneously, excessive accumulation of Cu⁺ ions within tumor cells triggers cuproptosis, a copper-dependent cell death mechanism. The MnPC component further enhances therapeutic efficacy by inducing DNA damage and suppressing cellular antioxidant defenses. Importantly, the nanosystem demonstrates selective toxicity toward cancer cells, sparing normal tissues and minimizing off-target effects. In vivo studies revealed significant tumor regression and

prolonged survival in tumor-bearing models, with no observable systemic toxicity.

Conclusions: This study successfully demonstrates the synergistic anticancer effects of CDT and cuproptosis through the design of a novel TCPP-Cu-MnPC nanosystem. By leveraging the unique biochemical features of the TME, this approach achieves highly efficient and selective cancer cell death while minimizing damage to normal tissues. The combination of ROS generation, cuproptosis induction, and DNA damage provides a multi-faceted mechanism for tumor suppression, offering a promising new strategy for precision cancer therapy.

Rapid systematic screening of bispecific antibody surrogate geometries for T-cell engagement using DNA nanotechnology

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Introduction: Bispecific antibodies (bsAbs) are a promising class of pharmaceutical that have found applications across various therapeutic areas including oncology, immunology, and infectious diseases. Over 100 different formats of multi-specific antibodies exist. These are generally based on the structure of immunoglobulin G (IgG) or its components, some having an Fc portion and others not. The vast majority of bsAb fall into broad categories such as IgG-like molecules, IgG conjugates, and conjugates of IgG fragments. Intriguingly, while the structures of these platforms differ considerably, little systematic data exists about how their geometry influences activity. As the complexity of these structures ever increases, implementing platforms based on surrogate scaffolds to rapidly de-risk and optimize antibody structures for different combinations of targets becomes important.

Methods: This presentation will showcase our efforts to exploit DNA nanotechnology to establish structure–activity relationships for bispecific antibodies. We will present a modular platform to rapidly prepare libraries of bispecific antibodies targeting CD19 and CD3 with surrogate geometries spanning ‘conventional’ formats. We study the basic question of whether the geometry of a bispecific antibody influences its activity. This is highly relevant and useful to guide the choice of the most suitable format from the onset of lead development.

Results: The first clinical bispecific “T-cell engager” (BiTE) is blinatumomab, which simultaneously binds CD19+ B-cells and CD3+ T-cells, thereby bridging them and potentiating a T-cell-induced cytotoxic effect. The CD19 and CD3 portions of blinatumomab were separately produced and grafted to DNA nanostructures, to produce libraries of hybrid bsAb. T-cell engagement experiments highlight interesting structure–

activity relationships regarding bsAb potency and selectivity and raise questions regarding the molecular phenomena underlying activity. Many bsAb both more and less potent/selective than blinatumomab (used as control) were observed, while maintaining the same mechanism of action. BsAb size, flexibility, valency, and shape all played a role on T-cell engagement. To elucidate some effects, the platform was paired with a simple mathematical model.

Conclusion: This work is thus one of the first to systematically investigate and reveal the importance of the spatial organization of bsAb components on activity and equally provides an accessible and convenient tool for rapidly mapping out such trends for other combinations of target epitopes. It can, for instance, be used to mix-and-match different combinations of antibody fragments to discover new bsAb of interest. The platform can also be used to determine, for a given set of targets, whether activity strongly or weakly depends on the structural parameter of the bsAb. It will be particularly interesting to explore different applications, such as targeting antigens on different cells, antigens on the same cell, epitopes on the same antigen, etc. The facility of implementing these studies makes this hybrid platform useful for accelerating the identification of surrogate bsAb leads and gaining mechanistic insight into their activity.

Ensuring Quality in Generic Pharmaceuticals: Dissolution Issues with Bulk Drug Powders

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Introduction: The safety and efficacy of pharmaceutical dosage forms depend on the quality of raw materials used in their production. In South Africa, where generic drug manufacturing is prevalent, manufacturers can access raw materials from various suppliers at different price points. This study investigates the dissolution problems associated with bulk drug powders used by generic manufacturers, focusing on the physicochemical properties that influence dissolution and bioavailability.

Methods: Various factors affecting drug dissolution are examined, including solubility, wettability, particle size distribution, crystal structure, and the presence of excipients. The study also explores the impact of manufacturing processes, storage conditions, and test variables on dissolution rates. Specific case studies on drugs such as chlorthalidone, glibenclamide, phenylbutazone, rifampicin, and carbamazepine are presented to illustrate the challenges faced by generic manufacturers. Dissolution rates were measured using compendial methods for each drug.

Results: The study highlights the importance of in vitro dissolution tests for immediate-release solid oral dosage

forms, such as tablets and capsules, to ensure consistent product quality and performance. The Biopharmaceutics Classification System (BCS) is discussed as a framework for understanding the relationship between drug solubility, permeability, and dissolution. The study emphasizes the need for establishing in vivo-in vitro correlations (IVIVC) to predict the bioavailability of drugs based on their dissolution profiles.

Conclusion: The findings suggest that particle size should be included as a critical parameter in bulk drug specifications to ensure compliance with pharmacopeial standards and accurately predict in vivo performance. Specific drugs such as chlorthalidone, glibenclamide, phenylbutazone, rifampicin, and carbamazepine were studied to illustrate dissolution challenges. Key issues included particle size, polymorphism, and wettability affecting dissolution rates. The study concludes that a more discriminative dissolution method is preferred for quality assurance, as it can detect potential changes in product quality before they affect clinical performance.

Injectable thermoresponsive hydrogel for controlled drug delivery and regenerative treatment of volumetric muscle loss

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Volumetric muscle loss (VML) remains a significant challenge in regenerative medicine due to the limited intrinsic repair capacity of skeletal muscle. This study presents an injectable 4D biomaterial system utilizing thermoresponsive poloxamer-based hydrogels (Poloxamer 407/188) integrated with Agmatine Sulfate (AgS) and Hyaluronic Acid (HA) to achieve precise spatiotemporal control over drug delivery and tissue regeneration. The hydrogel system exhibits dynamic, temperature-dependent sol-to-gel transitions, allowing for minimally invasive administration and localized, sustained release of bioactive agents. A factorial design approach optimized critical parameters, including gelation temperature (33–37°C, physiologically compatible), rapid gelation time (<60 seconds), and sustained AgS release (72% over 96 hours), leading to the selection of the optimized formulation (PA9). Real-time thermal imaging (FLIR ONE® Pro) confirmed precise controlled gelation, reinforcing the system's biomaterials paradigm. In vivo studies demonstrated significant functional recovery, evidenced by improved grip strength and stride length, enhanced muscle fiber organization and reduced fibrosis. The hydrogel's regenerative efficacy stems from the synergistic interaction between HA's extracellular matrix (ECM)-mimetic properties and AgS's anti-inflammatory and neuroprotective effects. This work advances bioinspired, stimulus-responsive biomaterials for controlled regenerative therapies, highlighting their translational potential in VML treatment. By

integrating smart material design, biological functionality, and innovative characterization techniques, this platform bridges materials science and regenerative medicine, contributing to the rapidly evolving field of biomedical applications.

Development and validation of an ELISA assay to determine the potency of *Androctonus Australis* hector antivenom

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Scorpion envenomation is a serious health problem in Africa, especially in Algeria. Immunotherapy is the only specific treatment for this envenomation, acting through antigen-antibody binding, this complex neutralizes toxins present in the venom. Throughout the production process of antivenom, several rigorous assays are carried out to ensure its effectiveness. One of these assays is the neutralizing capacity assay which evaluates the ability of antivenoms to neutralize the toxins of venom injected in mice. However, this in vivo assay has several disadvantages which are the death and suffering of a large number of mice; In addition to the inter-individual variability in these animals' response to the same experimental and environmental conditions. An in vitro assay based on enzyme-linked immunosorbent assay (ELISA) have been proposed by some researchers as an alternative assay.

The main objective of this study was to develop and validate an ELISA for the titration of antibodies in horse sera against *Androctonus australis hector* (Aah) venom. For this purpose, various adjustments were implemented to develop an optimal ELISA technique. Crude venom of Aah scorpion was used for coating. Three sera with low, medium and high neutralizing capacity were tested and the titers were determined by calculating the cut-off for each microplate. The validation process included an assessment of intra-assay and inter-assay variability, as well as an evaluation of specificity.

The findings of this study showed that the ELISA procedure obtained after numerous assays appears to be optimal, specific and reproducible within a defined dilution range. Future studies should focus on further exploring its potential integration into standard antivenom production protocols. This includes classifying horses as good or weak responders and investigating the correlation between in vitro and in vivo assays to determine antivenom potency.

Assessment of detoxification methods of cerastes cerastes viper venom for antivenom manufacturing

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Antivenom serotherapy is the only specific treatment of ophidian envenomation, particularly those caused by the *Cerastes cerastes* viper. Due to the high toxicity of the native venom of this species used as an immunogen during the production of antivenom, severe pathological effects may occur occasionally in serum-producing horses. The objective of this study was to determine the most efficient detoxification method of *Cerastes cerastes* venom, which allows an optimal immune response and reduced toxicity, with the aim of using it to immunize antivenom-producing horses. For this purpose, the toxicity of venoms treated with different physicochemical methods was tested on mice, and those that showed a good tolerance were subjected to immunogenicity analysis using double immuno-diffusion. Subsequently, four groups of rabbits were immunized with increasing doses of native venom, irradiated venom, acidified venom, and alkalized venom, respectively. The health of the animals during the immunization period was monitored through daily observations. After 48 days, the rabbits were bled, and the sera were collected. The neutralizing capacity was evaluated, and the biological parameters were analysed. The study showed that venom detoxification using acidification was the most efficient method, preserving its immunogenicity and increasing its neutralizing capacity compared to native venom. The results of this study suggest the use of acidification for detoxifying *Cerastes cerastes* venom, but this should be subjected to further testing.

A comparative study of immunization protocols against rabies virus in rabbits

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Antirabies seroprevention is the most specific treatment for rabies after exposition. It is part of the post-exposure

prophylaxis (PEP) for rabies. Rabies immunoglobulins (RIG) are obtained from horses or humans after their vaccination. The objective of this study was to determine the most efficient vaccine that may give the highest antibodies' titers and which allows an optimal immune response, with the aim of using it to immunize anti-rabies immunoglobulins-producing horses. The secondary objective was to confirm that these vaccines do not induce the production of anti-mouse anti-myelin antibodies that are noxious for human health.

For this purpose, different vaccine schemes were tested on rabbits. Five groups of rabbits were immunized with different immunizing solutions using three different vaccines. The health of the animals during the immunization period was monitored for 48 hours after each immunization for 28 days and the rabbits were bled every week after each immunization. The animals were euthanized at the end of the study to collect the necessary sera. The antibodies titers were quantified by Rapid Fluorescent Focus Inhibition Test (RFFIT) and anti-mouse antibodies were sought by Ouchterlony method.

The study showed that Pasteur Institute of Algeria (PIA) cell-based-attenuated vaccine was the most efficient scheme and confirmed the absence of anti-mouse anti-myelin antibodies in the animals sera.

The results of this study suggest the use of PIA cell-based vaccine to immunize rabies immunoglobulins-producing horses.

Developing an optimized purification process for scorpion antivenom manufacturing

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Introduction: Scorpion envenomation is a significant public health concern, particularly in developing countries including Algeria. The development of antivenoms requires effective production techniques that ensure safety, efficacy, and scalability. This work aimed to propose a purification process of scorpion antivenom (SAV) with optimized production yield, purity profile, efficiency and tolerance.

Methods: This work involved optimizing the pepsination duration and conducting comparative evaluations of precipitation methods, particularly focusing on ammonium sulfate precipitation – used at Pasteur Institute of Algeria – and caprylic acid fractionation. The study also included an evaluation of the relevance of differential thermocoagulation. The purification conditions that gave the best purity profile had been tested on a semi-industrial scale

and the product obtained subjected to activity, tolerance, toxicity and electrophoresis assays. An assessment of the production yield and time between the current purification method and the optimized method was also conducted.

Results: Caprylic acid fractionation was found to be a cost-effective and time-saving method compared to ammonium sulfate precipitation despite some technical challenges encountered during semi-industrial production, such as filter clogging and mixing difficulties, due to the low volume of the processed sera. While the caprylic acid process reduced production time from three days to one day, its neutralizing capacity did not surpass that of ammonium sulfate (26.67 and 27.8 LD50/mg protein, respectively). Also, the yield of the two methods adjusted to protein concentration was comparable (31%). The values were adjusted to protein concentration in order to disregard the effect of dialysis on the neutralizing capacity and the yield. Local safety and abnormal toxicity tests were conclusive.

Discussion: While caprylic acid fractionation offered production advantages, further optimization during process scaling-up and the validation of the final full-scale process are needed. Issues like filter clogging, mixing parameters and temperature control during process scaling-up need to be addressed to enhance yield and purity. Additionally, residual caprylic acid should be quantified to ensure safety.

Conclusion: Caprylic acid fractionation is a promising alternative to ammonium sulfate precipitation for SAV production, with time, labor and cost savings. However, further refinement and validation are essential before it can replace the traditional method at an industrial scale.

A novel antioxidant based on carrot-derived nanovesicles alleviates oxidative stress for the treatment of osteoporosis

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Introduction: Osteoporosis (OP) is a systemic bone metabolic disease characterized by low bone density and deteriorated bone microstructure. The imbalance between bone formation and resorption is the main cause of osteoporosis. Increasing evidence indicates that oxidative stress is one of the important pathogenic mechanisms of osteoporosis. Therefore, developing a novel antioxidant that can alleviate oxidative stress and restore osteoblast activity is a potential strategy for treating osteoporosis. Thus, this study aims to develop a novel antioxidant based on carrot-derived nanovesicles (CNs) to achieve mitochondrial functional reprogramming and restore osteoblast activity, thereby

improving oxidative stress and promoting effective bone remodelling, providing new ideas and solutions for the treatment of osteoporosis.

Methods: CNs were prepared using the extrusion method. The morphology, size distribution, and zeta potential of CNs were characterized by transmission electron microscope, dynamic light scattering, and nanoparticle tracking analysis. The stability of CNs under different pH, temperature, and batches was examined. The composition of CNs was identified by proteomic and non-targeted metabolomic analyses. The scavenging abilities of CNs at different concentrations against $\bullet\text{OH}$, $\text{O}_2\bullet^-$, H_2O_2 , and total antioxidant capacity were evaluated. The uptake efficiency of MC3T3-E1 cells and the intracellular uptake mechanism of CNs were investigated. An oxidative stress model was established by stimulating cells with H_2O_2 to examine the cell viability, intracellular Reactive oxygen species (ROS) levels, osteoblast differentiation, mineralization degree, and relative expression levels of osteogenesis-related genes under oxidative stress conditions with CNs. The effects of CNs on mitochondrial membrane potential, number, morphology, and mitochondrial oxygen consumption rate under oxidative stress were also assessed. The impact of CNs on cell apoptosis after H_2O_2 stimulation was detected. The mechanism of CNs in alleviating oxidative stress and restoring osteoblast activity was explored using eukaryotic transcriptome sequencing. Finally, an osteoporosis mouse model was established to evaluate the in vivo efficacy and safety of CNs.

Results: The CNs obtained in this study had a double-membrane structure, uniform size, and good stability. They exhibited excellent antioxidant properties and were rich in various bioactive components such as proteins, lipids, and organic oxides. The nanovesicles showed good dispersion and stability under normal physiological conditions. In the simulated acidic osteoporosis microenvironment, they aggregated into larger particles, enhancing their retention in osteoporotic bone tissue. CNs had good biocompatibility, high cellular uptake efficiency, and the ability to scavenge oxidative damage, improve mitochondrial function in osteoblasts, reduce apoptosis, and restore osteoblast activity. They regulated the oxidative stress homeostasis through the calcium signalling pathway and MAPK signalling pathway. CNs responded to the acidic microenvironment of osteoporosis, passively targeted to bone tissue for efficient accumulation, and had good in vivo safety, achieving the reversal of osteoporosis.

Conclusion: This study successfully constructed CNs as a novel nano-antioxidant to modulate the oxidative stress microenvironment, effectively scavenging ROS, alleviating oxidative stress, restoring mitochondrial function in osteoblasts, and promoting osteoblast differentiation, thereby helping to reverse osteoporosis.

Developing an innovative coamorphous salt formulation of telmisartan with amlodipine to enhance permeability and oral absorption

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Introduction: Coamorphous formulations represent a promising strategy for improving the solubility of poorly water-soluble drugs through intermolecular interactions. A hydrogen-bonding-based coamorphous system was developed to enhance drug solubility; however, it had little effect on the apparent permeability (Papp) of the drug. To overcome this limitation, the present study aimed to design a novel coamorphous salt that utilises ionic interactions to enhance drug permeability and absorption.

Method: Telmisartan (TMS), which contains an acidic functional group, was combined with the basic amlodipine (AML) to form a coamorphous salt. TMS and AML were precisely weighed at molar ratios of 3:1, 2:1, 1:1, 1:2, and 1:3 in 15 mL glass vials. Each sample was mixed using a vortex for five minutes. A mixed sample of 500 mg, along with three 10 mm diameter balls, was placed in a 25 mL vessel and ground using a vibrating ball mill at a frequency of 30 s⁻¹ for 120 minutes.

Results: Physicochemical characterisation using powder X-ray diffraction, differential scanning calorimetry, and solid-state nuclear magnetic resonance confirmed the formation of the coamorphous salt via ionic interactions between the amine group of AML and the carboxyl group of TMS at a 1:1 molar ratio. The coamorphous salt of TMS/AML promoted the partitioning of both drugs into octanol, suggesting increased lipophilicity due to their interaction. Furthermore, the coamorphous salt significantly enhanced the solubility of TMS (100 times greater than that of untreated TMS) while reducing the solubility of AML because of drug–drug interactions. Although the coamorphous salt exhibited reduced Papp in the permeation study under conditions with a thicker unstirred water layer (UWL) without stirring, permeability improved when the UWL was thinner with stirring. The oral absorption of TMS from the coamorphous salt increased by up to 4.1 times in comparison to untreated TMS, whereas AML absorption remained unchanged. While increased lipophilicity may present a challenge for diffusion through the UWL, this layer is typically thin in humans and animals due to the peristaltic action of the digestive tract. Additionally, dissociation of the coamorphous salt at the membrane surface may facilitate the partitioning of the neutral drug form into membrane cells more efficiently than untreated drugs.

Conclusion: Coamorphous salt formation offers a significant advantage in improving the membrane permeability and oral absorption of TMS, owing to enhanced solubility and a sustained supply of membrane-permeable free TMS at the membrane surface.

Precision chemo-immunotherapy for cancer: A tumor microenvironment-responsive nano-delivery system

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Background: Pancreatic ductal adenocarcinoma (PDAC) and colorectal cancer (CRC) present a significant challenge due to their devastating nature, poor prognosis, and increasing incidence, contributing substantially to global cancer mortality. Effective strategies are urgently needed to combat these formidable diseases.

Methods: In this innovative preclinical investigation, a combination of the VCP/p97 inhibitor CB, miR-i (a miRNA that promotes M1 macrophage polarization and suppresses EMT), and R, a TLR7/8 agonist, was encapsulated within solid lipid nanoparticles (SLNs). These SLNs were designed with targeting peptides for PD-L1, EGFR, and the endoplasmic reticulum, and further enveloped in a pH-responsive and charge-switching shell. The nanoparticles exhibited stable homogeneous size and zeta potential over 28 days at 4°C.

Results: The study demonstrated that the CB, miR, and R-loaded nanoformulation concurrently modulated critical pathways, notably affecting VCP/Bip/ATF6, PD-L1/TGF- β /IL-4, and TNF- α /IFN- γ /IL-1 pathways. This adaptable nanoformulation induced durable antitumor immune responses and effectively inhibited PDAC and CRC tumor growth in mice. This was achieved by enhancing T cell infiltration and dendritic cell maturation, while simultaneously suppressing regulatory T cells (Tregs) and tumor-associated macrophages (TAMs). Furthermore, comprehensive tissue distribution studies, biochemical assays, and histological examinations emphasized the enhanced safety profile of the protective shell and peptide-modified nanoformulations for CB, miR, and/or R in tumor-bearing mice.

Conclusions: This versatile nanoformulation facilitates tailored adjustment of the tumor microenvironment, thereby

optimizing the localized delivery of combined therapy. These compelling findings advocate for the potential development of a pH-sensitive, tumor microenvironment-responsive nanoformulation combining a VCP inhibitor, a PD-L1 inhibitor, and an immunoadjuvant, offering a promising combinatorial chemo-immunotherapy strategy for cancer treatment.

Bioequivalence study of sodium valproate and valproic acid extended release tablets in healthy human volunteers

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Introduction: Sodium valproate and valproic acid are narrow therapeutic index medications that are widely used as anticonvulsants. In the Nepalese market, various brands of these antiepileptics are available, and switching between these brands without confirming their bioequivalence can lead to loss of seizure control. This study aimed to evaluate the bioequivalence of sodium valproate and valproic acid extended-release tablet formulation manufactured by a Nepalese pharmaceutical company against a Reference formulation.

Materials and methods: We conducted an open-label, randomized, two-way crossover study with fifteen healthy adult human volunteers. A 7-day washout period was kept between the study periods. Serial blood samples were obtained at 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, 36, 48, 60, and 72 hours post-medication administration on each study day. The bioavailability was assessed using pharmacokinetic parameters including peak plasma concentration (C_{max}), time to reach maximum serum concentration (T_{max}), area under the serum concentration-time curve (AUC₀₋₇₂), and area under the serum concentration-time curve extrapolated to infinity (AUC_{0-∞}).

Results: The assessment of bioequivalence between the Test and Reference formulations was conducted utilizing the 90% confidence interval for the logarithmic transformed values of C_{max}, AUC₀₋₇₂, and AUC_{0-∞}. Following oral administration, the C_{max} of valproic acid was recorded as 31.589±7.294 µg/ml for the Reference formulation and 28.299±5.554 µg/ml for the Test formulation with the T_{max} values of 9.711±2.250 hours and 9.714±2.119 hours, respectively. Moreover, the 90% confidence intervals of the mean of the differences between the log-transformed values of AUC₀₋₇₂, and AUC_{0-∞} and C_{max} remained within the bioequivalence acceptable range of 80% to 125%.

Conclusion: The result indicates that the two study formulations are bioequivalent in terms of both the rate and extent of absorption and they may be considered interchangeable.

Optimization and evaluation of fast disintegrating tablets containing *Fructus Ligustri Lucidi* extracts prepared by the direct compression method

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Background: *Fructus Ligustri Lucidi* (FLL) is a widely used traditional Chinese medicine known for its diverse pharmacological activities, including antioxidant, anti-inflammatory, and immune-modulating effects. FLL is widely used to treat hepatitis, diabetes, hyperlipidemia, and menopausal syndrome in clinical practice. Oleonic acid (OA), the primary active component of FLL, exhibits poor water solubility, which results in a slow dissolution rate, limited gastrointestinal absorption, and low bioavailability, thereby restricting its clinical applications. Fast disintegrating tablets (FDTs) are an innovative dosage form that disintegrates rapidly upon contact with saliva, offering convenient administration without the need for water and ensuring rapid onset of action.

Purpose: This study aimed to enhance the solubility of OA using the solid dispersion method. PEG 4000 and PEG 6000 were employed as matrix materials, while Tween 80 was used as a surfactant to investigate their potential to improve OA solubility. The optimal formulation was then developed into fast disintegrating tablets (FDTs) to improve bioavailability.

Materials and Methods: FLL extract was combined with PEG 4000, PEG 6000, and Tween 80 in various ratios to obtain the solid dispersion of FLL extract (FLLSD). The resulting FLLSD was dissolved, and high-performance liquid chromatography (HPLC) was utilized to identify the formulation that most effectively enhanced OA dissolution. The selected FLLSD was then mixed with effervescent materials, croscopidone, mannitol, and microcrystalline cellulose in different ratios, and FDTs were prepared using the direct compression method. The physical properties of the tablets, including breaking force, friability, wetting time, and disintegration time, were measured to evaluate the impact of formulation variables. To ensure a comprehensive investigation, a 2³ full factorial design was employed for both FLLSD and FDTs formulation screening.

Results and Discussion: Three variables were found to positively affect the solubility of OA. In addition, the inclusion

of Tween 80 was particularly important for the release of OA, especially when the ratio of PEG 4000/PEG 6000 was reduced. Regarding the physical properties of FDTs, the results showed that increasing the content of microcrystalline cellulose enhanced the breaking force of FDTs, while increasing the content of effervescent materials had the opposite effect. For friability, an interaction between effervescent materials and croscopidone was observed. At lower levels of effervescent material contents, croscopidone positively affected friability, while at higher levels, croscopidone negatively impacted friability. Furthermore, the content of croscopidone was identified as the main effective variable in FDT disintegration, as increasing its content significantly reduced the disintegration time.

Conclusion: This study successfully employed the solid dispersion method to produce FLL FDTs, significantly improving the water solubility of FLL extracts. The optimal formulation of FDTs disintegrated within 30 seconds. This study contributes to the development of more innovative dosage forms, thereby enhancing the bioavailability of FLL.

Combined blockade of lipid uptake and synthesis by CD36 inhibitor and SCD1 siRNA is beneficial for the treatment of refractory prostate cancer

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Introduction: Drug resistance is a key factor in the progression of prostate cancer (PCa) to refractory PCa, and abnormal lipid metabolism frequently occurs in refractory PCa. These abnormalities can affect biological functions such as proliferation, metastasis, and drug resistance in PCa, thereby exacerbating the progression and spread of PCa and eventually progressing to refractory PCa, posing significant challenges to its treatment. In this study, a cluster of differentiation 36 (CD36) inhibitor, sulfosuccinimidyl oleate sodium (CD36i), and stearyl-CoA desaturase 1 (SCD1) siRNA (siSCD1) are utilized to inhibit lipid uptake and synthesis in PCa, respectively.

Method: To achieve this, a multiresponsive drug delivery nanosystem, HA@CD36i-TR@siSCD1, has been designed. The hyaluronic acid (HA) gel "shell" of the HA-TR nanosystem enables drug release in response to the acidic tumour microenvironment and hyaluronidase, while the tumour-targeting (TR) cationic micellar "core" facilitates drug release in response to glutathione. This multiresponsive drug release strategy supports the exogenous inhibition of lipid uptake by CD36i and the endogenous inhibition of lipid synthesis by siSCD1. The HA@CD36i-TR@siSCD1 nanosystem was constructed and evaluated, and then the in vitro and in vivo

transport mechanisms of HA@CD36i-TR@siSCD1 was investigated. In addition, the Enz-resistant cell Lines C4-2BEnz and RM-1Enz were selected for the following study, and 2D/3D cell models with or without high concentrations of OA as well as low-fat diet (LFD)-fed and high-fat diet (HFD)-fed mouse models were established to investigate the efficacy and safety of HA@CD36i-TR@siSCD1 in vitro and in vivo, with the goal of providing a new treatment option for patients with refractory PCa, especially obese patients on a HFD.

Results: The developed multi-responsive HA-TR nanosystem demonstrates strong tumour-targeting and penetration capabilities. The HA gel shell can actively target CD44 expressed on tumor cells and depolymerize in response to the acidic tumor microenvironment and hyaluronidase, while TR@siSCD1 micelles can target PCa cells with the guidance of the RGD peptide and release siSCD1 in response to intracellular GSH and the proton sponge effect. HA@CD36i-TR@siSCD1 exhibits effective synergistic effects, significantly suppressing the growth, invasion, and metastasis of PCa. Furthermore, under high-fat conditions, tumours show heightened sensitivity to HA@CD36i-TR@siSCD1 treatment. Notably, almost no lipid droplet accumulation is observed in HA@CD36i-TR@siSCD1-treated tumours, most lipids were downregulated, especially in HFD-fed mouse tumors. Moreover, the immune microenvironment of tumor in mice, especially in HFD-fed mice, transformed from “cold” to “hot”, with increased CD8+ T cells, decreased CD4+FoxP3+ Treg cells, as well as elevated levels of tumor killer factors TNF- α and IFN- γ . In addition, the developed HA-TR nanosystem showed good biocompatibility and safety both in vitro and in vivo, indicating a good clinical translational value.

Conclusion: This study, therefore, offers a novel therapeutic approach based on lipid metabolism regulation for refractory PCa patients, particularly for patients with a high-fat diet.

Development and evaluation of biodegradable hydrogel-based bioadhesive for tissue engineering and surgical applications

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Dr. Prashant Sahu currently serving as Assistant Professor in Department of Pharmaceutical Sciences, Dr. Harisingh Gour Central University, Sagar, MP, India and was a former Associate Professor in BTIPS College Sagar. He was also a CSIR sponsored Research Associate, and ICMR sponsored Senior Research fellow in Department of Pharmaceutical Sciences, Dr. Harsingh Gour Central University, Sagar, MP. He obtained his PhD from the same University in 2018. He completed his Bachelor's (2010) and Master's degree in honors (2012) from Sagar Institute of Pharmaceutical Sciences, Sagar, M.P. and

served as Assistant Professor in the same institute and actively engaged in research work which he proceeds after enrolled in PhD in the field of Nanomedicine. He has 40 research article in high impact journal and 8 Patent. Dr. Prashant is also an author of 4 books (2 National and 2 International publishers) and published 6 international book chapters. He also won many international and national level oral & Poster presentation award along with prestigious MPCST 2017 YOUNG SCIENTIST AWARD. He has also delivered his research lecture in international conferences abroad in (78 FIP) United Kingdom (2018) and (79 FIP) United Arab Emirates (2019). His current project focused on the topical and Transdermal nanocarrier delivery obtaining biodegradable and biocompatible novel nano candidates against cancer.

Automated Production of 18F-FDG: Targeted Cyclotron Production and Quality Control Procedures in South Africa

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Introduction: The expanding field of positron emission tomography (PET) radiopharmaceuticals, particularly fluorine-18-labeled fluorodeoxyglucose (¹⁸F]F-FDG), is driven by advances in functional imaging and molecular diagnostics. As clinical demand increases, the need for efficient, reproducible production processes and rigorous quality control becomes critical to ensure patient safety and diagnostic accuracy.

Method: An automated synthesis module was employed to produce [¹⁸F]F-FDG via nucleophilic radiofluorination of a mannose triflate precursor. The reaction parameters, including temperature, time, and reagent concentrations, were optimized to maximize radiochemical yield and minimize impurities. Post-synthesis, the crude product was purified through solid-phase extraction and/or chromatographic methods. The final formulation was adjusted for clinical suitability and underwent a comprehensive battery of quality control tests, including assessments of radiochemical identity and purity, chemical purity, radionuclidic identity and purity, sterility, and endotoxin levels.

Results: The automated process consistently produced high-purity [¹⁸F]F-FDG, meeting clinical standards. Radiochemical identity and purity were confirmed by chromatographic comparison with reference standards, while chemical purity was verified through gas chromatography and high-performance liquid chromatography. Radionuclidic assessments confirmed the exclusive presence of fluorine-18. Sterility and pyrogen testing validated the product's safety for human injection. The automation also significantly reduced synthesis time and personnel exposure to radiation.

Conclusion: Automated production and quality control of [¹⁸F]F-FDG are essential to support the increasing clinical demand for PET imaging. Automation ensures reproducibility, efficiency, and safety, while comprehensive quality control guarantees product integrity. Adherence to stringent manufacturing protocols and validation of each production step are vital for delivering reliable, high-quality radiopharmaceuticals for diagnostic use.

Paracetamol quantum dots: A revolutionary leap in nanomedicine and drug delivery

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Introduction: Paracetamol, a widely prescribed analgesic and antipyretic drug, exhibits limited anti-inflammatory activity. It is classified as a Class III drug and its absorption is constrained by low permeability, resulting in reduced bioavailability. Consequently, advanced drug delivery systems are increasingly employed to enhance its therapeutic efficacy. Quantum dots (QDs), particularly carbon quantum dots (CQDs), have emerged as promising candidates. Conventional QDs, composed of heavy metals, raise significant toxicity concerns. CQDs, derived from carbon, offer advantages such as facile synthesis, environmental sustainability, minimal cytotoxicity, and excellent biocompatibility. Their tunable optical properties are also suitable for diverse biomedical applications, including drug delivery and bioimaging. Recent advancements have focused on synthesising CQDs directly from active pharmaceutical ingredients, offering improved bioavailability, reduced toxicity, and enhanced solubility. This research aimed to synthesise paracetamol carbon quantum dots (PSCQDs) directly from paracetamol and evaluate their physicochemical properties, cytotoxicity, and in vitro release profile. The objective was to assess the potential of PSCQDs as an enhanced drug delivery system. Characterization studies, including particle size, polydispersity index (PDI), zeta potential, and quantum yield (QY%), were conducted, alongside cytotoxicity assays, in vitro release studies, and stability tests.

Methods: PSCQDs were synthesised using a microwave-assisted method. Using dynamic light scattering, the synthesised nanoparticles were characterised for particle size (PS), PDI, and zeta potential (ZP). Quantum yield (QY%) was determined via spectrofluorometry. Cytotoxicity was evaluated using the MTT assay on a keratinocyte cell line. In vitro release studies were performed using Franz diffusion cells with a pH 7.4 phosphate buffer at 37 °C. Stability tests were conducted, and the obtained data were statistically analysed using analysis of variance (ANOVA).

Results: Upon exposure to 365 nm UV light, the PSCQDs exhibited bright blue fluorescence, indicating successful synthesis. The PS was determined to be 8.78 nm, with a PDI of 14.6 and a ZP of -15.1 mV. The QY% was calculated to be 87.8%. Cytotoxicity assays revealed a significant reduction in toxicity compared to the control group. In vitro release studies demonstrated a significantly improved release profile for PSCQDs compared to paracetamol alone. These findings suggest that encapsulating paracetamol within CQDs enhances its cellular effects.

Conclusion: The PSCQDs exhibited increased efficiency at lower doses and reduced cytotoxicity, demonstrating their potential as a promising drug delivery system. The direct synthesis of CQDs from paracetamol offers a feasible approach for enhancing its therapeutic efficacy and imaging capabilities. These results suggest that PSCQDs hold significant promise for therapeutic and diagnostic applications. Further detailed findings will be presented in the oral presentation.

FePt-incorporated metal-organic framework nanoparticles for drug delivery and sonodynamic therapy

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Background: Cancer remains a major global cause of death, and novel treatment strategies are being developed. Sonodynamic therapy (SDT) is a promising cancer treatment but is constrained by hypoxia and excess H₂O₂ levels that are prominent in tumor cells. Nanomedicines such as metal-organic frameworks (MOF) can not only enhance SDT by carrying compounds to generate oxygen and decomposed H₂O₂, but also can be modified to deliver anticancer drugs which together will result in synergistic anticancer therapy.

Purpose: Herein, we have synthesized FePt@MIL-125-NH₂-Pt(IV) nanomedicine for combined chemodynamic and sonodynamic therapy. The FePt core induces ferroptosis, while its Pt component catalyzes H₂O₂ degradation to

generate O₂, enhancing SDT under ultrasonic wave irradiation (USWI). MIL-125-NH₂, a semiconducting MOF, produces reactive oxygen species (ROS) via electron-hole pair separation under USWI. Lastly, Pt(IV) prodrug being conjugated to the MOF will be released intracellularly to chelate DNA to inhibit cell proliferation. The combined effects lead to a multimodal anticancer approach.

Method: FePt-cysteine nanoparticles were synthesized via reduction, followed by a solvothermal reaction with DMF to form FePt@MIL-125-NH₂. Pt(IV) prodrug was then conjugated via amide bonding to finally obtain FePt@MIL-125-NH₂-Pt(IV). The nanomedicine was characterized and assessed for O₂ generation, ROS production, drug release, cellular uptake, and antitumor efficacy both in vitro and in vivo.

Results: The synthesized nanomaterial had a 170 nm particle size. PXRD confirmed the crystallinity of FePt and MIL-125-NH₂ components, while FTIR validated Pt(IV) prodrug conjugation. Zeta potential shifted from -16 mV (FePt@MIL-125-NH₂) to -12 mV (FePt@MIL-125-NH₂-Pt(IV)), indicating successful conjugation. The nanomedicine showed a threefold increase in O₂ generation after 450 s, and ROS was observed to be generated inside 4T1 cancer cells via confocal microscopy. MTT assays revealed that the IC₅₀ of FePt@MIL-125-NH₂-Pt(IV) is 42.5 µg/mL, with 75% of 4T1 cancer cells killed at 90 µg/mL. In the cells treated with FePt@MIL-125-NH₂-Pt(IV) under USWI, complete cell eradication was observed. In vivo, tumor size was reduced threefold within two weeks after in situ administration (4 mg/kg) with USWI without affecting the relative size of mice, thus suggesting that no adverse drug reactions took place.

Conclusion: FePt@MIL-125-NH₂@Pt(IV) nanomedicine effectively combines chemodynamic and sonodynamic therapy to combat cancer. The current properties are indicators for a promising potential in clinical use.

Co-amorphous system of aprepitant and naringin: Enhanced solubility, bioavailability, and cytotoxicity for potential lung cancer treatment

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Introduction: Poor aqueous solubility and low bioavailability remain major challenges in the oral delivery of Aprepitant (APT), limiting its therapeutic potential. Co-amorphous systems (CAMs) have emerged as a promising strategy to enhance solubility and bioavailability by stabilizing the amorphous form of drugs through intermolecular interactions. However, limited research has explored the co-

amorphization of APT with bioactive cofomers for synergistic effects. This study investigates the co-amorphous system of APT with Naringin (NARI) as a novel approach to improve solubility, dissolution, and therapeutic efficacy while providing potential anticancer benefits.

Purpose: This study aims to develop and characterize APT-NARI CAMs to enhance APT's solubility, dissolution rate, and bioavailability. Additionally, the study evaluates the cytotoxic potential of APT-NARI CAMs against A549 lung cancer cells, hypothesizing that NARI, as a bioflavonoid cofomer, may contribute to improved therapeutic outcomes.

Method: APT-NARI CAMs were prepared using the solvent evaporation method at different molar ratios (1:1, 1:2, and 2:1). Solid-state characterization was conducted using differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), Fourier-transform infrared spectroscopy (FTIR), and scanning electron microscopy (SEM) to confirm co-amorphization. Molecular dynamics (MD) simulations and density functional theory (DFT) calculations were employed to analyze intermolecular interactions, phase transitions, and electronic properties. Solubility and dissolution studies were performed in simulated gastric fluid. The pharmacokinetic profile of the optimized APT-NARI CAM (1:2 molar ratio) was evaluated in vivo by measuring AUC_{0-t} and C_{max}. Cytotoxicity against A549 cells was assessed using the MTT assay.

Results: The formation of co-amorphous APT-NARI was confirmed by the disappearance of crystalline peaks in PXRD and the presence of a single T_g in DSC analysis. Among the formulations, APT-NARI at a 1:2 molar ratio exhibited the highest solubility, with a 4.8-fold increase compared to amorphous APT, followed by the 2:1 (4.2-fold) and 1:1 (4.1-fold) ratios. Pharmacokinetic studies demonstrated a 2.4-fold increase in AUC_{0-t} and a 1.4-fold increase in C_{max} for the 1:2 APT-NARI CAM compared to the physical mixture. Cytotoxicity assays indicated enhanced anticancer activity of the APT-NARI CAM against A549 cells, suggesting potential therapeutic benefits.

Conclusion: This study demonstrates that co-amorphization of APT with NARI significantly enhances solubility, dissolution, and bioavailability, while also exhibiting improved cytotoxicity against lung cancer cells. The findings highlight the potential of cofomer-based CAMs as a promising approach for developing stable and high-performance drug formulations. Future research should explore the mechanistic insights of APT-NARI interactions and assess the in vivo anticancer efficacy of the optimized formulation.

Synthesis, characterization, and biodistribution of boron-doped carbon quantum dots: Advancing biocompatible nanomaterials for targeted biomedical applications

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Introduction: Quantum dots with 1-10 nm dimensions are a member of zero-dimensional nanomaterials. They exhibit unique properties due to their size. Their continuous luminescence, easy passage through biological barriers, and use as drug carriers make quantum dots a critical potential in the field of health. However, the luminescence properties and surface chemistry of quantum dots have not yet been fully elucidated. Recent research has focused on the production of biocompatible and low-toxic quantum dots. While the first developed quantum dots consist of a metal-based core, carbon-based quantum dots have been developed in recent years. Carbon quantum dots have low toxicity, high biocompatibility, and good photostability. Heteroatoms such as boron, nitrogen, and sulphur can be added to carbon quantum dots. Doping with boron changes the physical and chemical properties of carbon quantum dots and makes them more stable. Boron composite carbon quantum dots can be used in drug targeting, as imaging agents or in biosensors such as others. Our aim in our study is to produce quantum dots synthesized from different starting materials, to develop their formulations and to examine their biodistribution. Thus, quantum dots will be produced in optimized doses suitable for use and their potential for use and targeting in the health field will be evaluated.

Methods: Boron-doped carbon quantum dots were synthesized using the microwave synthesis method. After synthesis, purification by column chromatography and PEG coating processes were applied. pH, particle size, zeta potential, and fluorescence properties were analysed for characterization. Stability studies were performed under different temperature and humidity conditions. Biocompatibility, toxicity, and biodistribution analyses were performed in in vitro and in vivo experiments.

Results: The obtained data revealed that the physical and chemical properties of the synthesized quantum dots differ

depending on the starting materials. Significant differences were observed between particle size, zeta potential, and fluorescence properties. It was determined that PEG coating increased the stability and biocompatibility of quantum dots. As a result of in vivo analyses, biodistribution differences were revealed in intravenous, intraperitoneal, and oral applications and it was observed that quantum dots were distributed in different densities in various tissues. While faster distribution and elimination were observed in IV applications, slower and longer bioavailability was observed in PO applications. In addition, it was determined that quantum dots showed intensive accumulation, especially in liver and kidney tissues. In stability studies, changes in the physical and chemical properties of quantum dots were observed depending on different storage conditions and it was concluded that stability was lower at room temperature.

Conclusion: It was concluded that the biodistribution of boron-doped quantum dots may differ depending on the starting materials and application routes. This study will guide future studies on the use of boron-doped quantum dots as drug delivery systems and bioimaging agents. This study was supported by the TUBITAK with project number 122S595.