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CONFERENCE ABSTRACTS

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Drug delivery and manufacturing

Development and stability evaluation of a hydrophilic gel containing a coenzyme Q10-loaded nanoemulsion

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Coenzyme Q10 (Q10) has been successfully applied in medicine, cosmetics and nutraceuticals, i.e., it shows high effectiveness in the treatment of neurodermatitis, psoriasis, periodontitis, external substitution under stress, adiposity, immune support, etc. Coenzyme Q10 is a highly effective liposoluble antioxidant, possessing radical scavenger and bioenergetical properties. Thus, Q10 is highly effective in preventing photoageing in vivo with a reduction in wrinkle depth. Because of its antioxidant activities against environmental aggressions and photoageing, Q10 has been frequently used in cosmetic anti-ageing products.

The aim of this study was to develop and characterize a semisolid gel formulation containing lipid nanocarriers, i.e., a nanoemulsion loaded with coenzyme Q10 in order to enhance its stability as Q10 is easily oxidized, especially under aerobic conditions and light exposure. Q10 has been mostly incorporated into solid lipid nanoparticles (SLN) or nanostructured lipid carriers (NLC) to increase its stability. However, in this study a nanoemulsion has been loaded with Q10 and further incorporated into carbomer hydrogel.

A Q10-loaded (0,5% w/w) nanoemulsion was prepared from caprylic/capric triglycerides (15% w/w), non-hydrogenated lecithin (6,6% w/w), ethanol (10% w/w), characterized for its particle size, polydispersity index (PDI), zeta potential, pH value and Q10-content. Afterwards the nanoemulsion was incorporated into a hydrophilic carbomer gel. The Q10-nanoemulsion-containing gel and the Q10-conventional gel were analyzed for flow properties by continuous rheology measurements, for pH values and Q10-content, 48 h after preparation and after a temperature stress test (5 cycles were performed; 1 cycle: 24 h at 4oC, 24 h at 20±2oC and 24 h at 45oC), in order to predict the long term stability.

The oil drops of the Q10-loaded nanoemulsion were of small particle size (307.4±0.7 nm) and negative zeta potential (-53.2±1.1 mV), the emulsion was homogeneous (PDI=0.27±0.006) and the Q10-content was 99.7% from the required content (this determined content was set as 100%). The obtained nanoemulsion was incorporated into the gel, thereby leading to a Q10-nanoemulsion gel, which showed as well as the conventional Q10-gel a non-Newtonian, shear-thinning plastic flow behavior. Both gels possessed and mild acid pH value, i.e., 6.08±0.05 the nanoemulsion gel and 6.00±0.03 the conventional gel. The temperature stress test revealed that temperature changes did not change the organoleptic properties of the gels, they did not

significantly influence the pH value ($p>0.05$), while they significantly decreased Q10-content ($p<0.05$) in gels. However, Q10 was significantly more ($p<0.05$) stable in the nanoemulsion gel than in the conventional gel. Rheological parameters significantly changed in the conventional gel, in contrast to the nanoemulsion gel. However, no changes, which occurred in both gels, would indicate low stability of the gels.

In conclusion, the obtained Q10-loaded nanoemulsion gel was suitable for its topical use onto the skin due to its rheological properties and pH value, and could serve as a delivery system for Q10. The Q10-nanoemulgel exhibited sufficient stability even after performing a temperature stress test.

Development of hydrophilic gel containing methanol extract of *Cotinus coggygria* stem with bark

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Cotinus coggygria Scop., Anacardiaceae (smoke tree) has been used in traditional medicine for its antioxidant, anti-inflammatory, antiseptic, antihaemorrhagic activity.
The aim of this study was to develop a gel containing the extract of Cotinus coggygria, which could be used for wound healing, treatment of Acne vulgaris and aphthous stomatitis. However, before the incorporation of the plant extract into the gel, the first stage of the hydrogel development included a chemical characterization of the extract.
The whole plant of Cotinus coggygria was collected in Bosnia, during July 2022. For the extraction the stem with bark of the plant was used, while methanol was used as the extraction solvent. Powdered samples were extracted using heated water bath, afterwards filtered and evaporated to dryness.

The quantitative determination of compounds contained in the extract was performed by HPLC using reverse-phase chromatography and gradient elution. According to the results the dominant compound was fisetin (22.79 mg/g dw) followed by quercetin derivatives hyperoside and isoquercitrine (5.62 mg/g dw and 2.21 mg/g dw). Having in mind phenolic acids, gallic acid, chlorogenic acid and caffeic acid were also determined and their amount was as follows: 1.17, 0.90 ad 0.57 mg/g dw, respectively.

After the HPLC analysis of the methanol extract of Cotinus coggygria, the extract was incorporated into an optimized hydrophilic gel. The ratio of carbomer and poloxamer 407 was varied and the optimal gel was prepared, as follows: carbomer (0.15%, w/w) was dispersed in purified water by mechanical stirring. Afterwards, Poloxamer 407 (20.0%, w/w) was added to the carbomer dispersion. This mixture was kept overnight (12 h) to ensure complete hydration of the gelling agents. The next day the dispersion was stirred by a mixer to ensure complete mixing of the two polymers, and 5% w/w of the dry plant extract was added. Finally, the 10% w/w solution of TEA was added for neutralization.
The prepared hydrogel containing the Cotinus coggygria extract possessed suitable properties for topical application onto the skin and oral mucosa.

Harnessing the synergistic potential of 3D printed buccal films and nanostructured lipid carriers (NLCs) for personalised cannabidiol delivery

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Background: Cannabidiol (CBD) has been recognized for its numerous therapeutic benefits, such as neuroprotection, anti-inflammatory effects, and cardio-protection. Unlike its psychoactive counterpart, Tetrahydrocannabinol (THC), CBD is non-hallucinogenic and has low toxicity and high tolerability. However, CBD has some limitations, including unpredictable pharmacokinetics and low oral bioavailability. Therefore, there is a growing need for a delivery system that can effectively address these concerns. In recent years, 3D printing, and buccal films have gained considerable attention in the pharmaceutical field. Additionally, lipid-based formulations, such as Nanostructured Lipid Carriers (NLCs), are considered a promising approach to enhancing the solubility and bioavailability of poorly water-soluble drugs. Also, the Box-Behnken design is a widely used optimization method in pharmaceutical research, as it allows for fewer runs and less time than other methods. Purpose: We employed Design of Experiments (DoE), lipid carriers, and 3D printing techniques to optimize and develop buccal film loaded with CBD-NLCs to overcome challenges associated with CBD delivery.

Methods: Three-factor Box-Behnken Design was carried out to optimize the NLCs and analyse the effect of independent factors on dependent factors. The NLCs were prepared by the emulsification-ultrasonication method. The investigated independent variables were (X1) total lipid concentration (% w/v TL), (X2) surfactant concentration (v/v %), and (X3) ultrasonication time (min) whereas particles size (Y1), and polydispersity index (Y2) were chosen as dependent variables. Pressure-assisted micro-syringe printing technique was used to produce the films. The produced films were studied for physicochemical, mechanical properties, release profiles, and in vivo performance.

Results: The observed particle size of the NLCs ranged from 12.17 to 84.91nm whereas the PDI varied from 0.099 to 0.298. Lipid and sonication time positively affected the particle size whereas the surfactant concentration was inversely related. Total lipid concentration had a prominent effect on particle size. The numerical optimization process indicated the optimal NLC composition with 2% total lipid (X1), 5% surfactant concentration(X2), and (X3) 4.5 min sonication time. CBD was incorporated into the optimal formulation and the observed particle size, PDI, and zeta potential for the CBD-NLCs was 94.2 ±0.47nm, 0.11± 0.01 and−11.8 ± 0.52 mV. Hydroxyethyl cellulose (HEC)-based gel containing the CBD-NLCs was used as a feed for 3D printing.

The 3D-printed film was smooth and flexible. CBD-NLCs film depicted a biphasic release pattern characterized by a relatively faster initial burst release (47% in 2h) followed by comparatively slower and continuous release (84. 11 ± 7.02% in 6h). The predicted AUC0–10h, Cmax, and Tmax were 201.5µg·h/L, 0.74 µg/L, and 1.28 h for a film loaded with 0.4 mg of CBD, respectively.

Conclusion: The finding demonstrates that the buccal film of CBD-NLCs that potentially improve unpredictable pharmacokinetics, the low bioavailability of CBD, and aids individualized therapy can be produced using 3D printing.

pH-responsive Inulin Hydrogel Loaded with 5-FU for colon target delivery

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Introduction: 5-Fluorouracil (5-FU) is a commonly used chemotherapeutic agent for colon cancer treatment. However, its clinical utility is constrained by systemic toxicity and off-target effects. Optimizing drug delivery to the target site while minimizing systemic side effects is a major challenge in the treatment of colon cancer using chemotherapeutic agents. To overcome the drawbacks associated with conventional 5-FU formulations, it is necessary to develop a suitable drug delivery platform that can facilitate localized and targeted delivery of 5-FU to the colon, thereby reducing its toxicity.

Purpose: To carry out the extensive physicochemical characterization of the 5FU-loaded inulin hydrogels

Method: Drug-loaded 5-FU inulin hydrogels were prepared by crosslinking inulin with pyromellitic dianhydride (PMDA) using triethylamine as a catalyst[1]followed by loaded of the 5-FU using the swelling method. The drug-loaded hydrogels were characterized using Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), Scanning Electron Microscope (SEM), as well as degradation, in-vitro release, and biocompatibility tests.

Result and Discussion: The study confirmed that 5-FU was successfully encapsulated within the hydrogels using FTIR with absorption bands at 3071, 1246, 1433, and 750 cm^1, XRD indicates the formation of amorphous materials and alteration in the crystalline structure of 5-FU within the hydrogel. SEM was used to confirm the porous structure within the polymeric gel and that 5-FU was encapsulated within the pores. 5FU loading from 8.2-18.0 %, was achieved through the modulation of the PMDA crosslinker ratio. In addition, the in-vitro release was pH-dependent and by varying the ratio of the crosslinker PMDA the release rates of 5-FU from the hydrogels can be tuned. Despite crosslinking, the hydrogels exhibited outstanding enzymatic biodegradability. The efficacy of the 5-FU-loaded hydrogel against HCT116 colon cancer cells was found to be concentration-dependent.

Conclusion: Based on the findings, the hydrogels loaded with 5-FU have great potential as a delivery system for targeted and localized administration of 5-FU to the colon.

Spray-drying technique retains the alpha-glucosidase inhibitory activity of ethnopharmacological plants

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Numerous pharmacologically active phytochemicals for diabetes are discovered annually. The stability and activity of phytochemicals intended to be active pharmaceutical ingredients (APIs), however, are not warranted under normal storage conditions to subject them to FDA-required preclinical and clinical tests sustainably.

Spray-drying is the preferred technique employed to transform liquid pharmaceutical preparations, especially herbal medicinal extracts, into a dry powder form. This method offers several advantages; i.e., it offers good potential for scalability, can run continuously and efficiently, has better solubility and dispersibility, and has enhanced stability over liquid dosage forms.

A 23-full factorial design was executed to identify the optimal parameters to produce a stable spray-dried extract (SDE). Air-dried leaves were macerated in ethanol and exhaustively concentrated using a rotary evaporator. A benchtop spray dryer and spray drying carrier (e.g., maltodextrin and gum arabic) were used to prepare the spray-dried extract powders. Spray drying parameters were variably operated to produce the ideal SDE.

The pharmacologic activity of the prepared SDEs was based on their inhibitory activity on alpha-glucosidase and the production of p-nitrophenol quantified at 405 nm. The assay was performed under continuous kinetic measurements with four replicates.

Ideal spray-drying carriers for plants 009L and 045A were determined to be maltodextrin and gum arabic, respectively. Plants are coded to protect the potential intellectual property rights arising from the study. SDEs of 009L and 045A had acceptable hygroscopicity values of 8% and 2%, respectively. At 10 ppm, the ethanolic sample of plant 009L and its SDE had 99.79 ± 0.011 and 99.84 ± 0.005 (MD) inhibitory activity on alpha-glucosidase, respectively.

Furthermore, at a lower dose of 1 ppm, no reduction in the inhibitory activity of 009L SDE was observed. In the ethanolic sample of 045A, the inhibitory activity was 7.85% ± 3.5 while its SDE had 8.19-fold higher activity (64.29% ± 3.64). Acarbose (1000 ppm), positive control, had 84.04 ±0.52 inhibitory activity.

Spray-drying of scarce ethnopharmacological plants produces APIs that are stable and maintain or enhance their pharmacologic activity against alpha-glucosidase ensuring completion of required pharmacopeial and pre-clinical testing.

Formulation and characterization of niosomal gel for topical delivery of ceftazidime against staphylococcus aureus and methicillin resistant staphylococcus aureus

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Skin infection are among the most common disorders found in the community and hospital environments. These can present in a variety of forms, ranging from limited superficial infections to serious infection that are controlled by treatment with topical antibiotics.
Topical antibiotic use offers several advantages over systemic administration, including delivery of high concentrations of antimicrobial at the required site of action and a reduction in systemic toxicity. However, the widespread use of commonly used topical antibiotics (particularly mupirocin and fusidic acid) has led to increasing bacterial resistance in some settings, limiting the potential efficacy of such agents.
The limited advancement in the topical administration hampered the possibilities of avoiding severe infections of deep tissues that sometimes leads to death if not appropriately treated.
The study prepared various formulation of gel and it was observed in terms of physicochemical parameters of a formulated gel. The pH, viscosity, spreadability, homogeneity, extrudability and content uniformity were observed to ensure that the formulated gel follows the parameter required. It was then subjected to compatibility testing using Fourier Transform infrared spectroscopy which showed that the Niosome loaded gel formulations are comparable with the significant IR Bands found in the gel base that is not loaded with niosome. This meets the primary goal of the study to encapsulate the niosome and gel components after formulation.

The formulation was subjected to comparative antimicrobial assay and further assessed the activity of Niosomal gel formulation 1,2 and 3 against the antimicrobial activity of Vancomycin which is the standard drug for MRSA and Mupirocin which is the drug of choice for MRSA skin infections. The formulation all exhibited a zone of inhibition comparable with vancomycin. The commercially available mupirocin showed more potential in terms of activity but in terms concentration, the Niosomal gel formulation that has a lower dosage strength compared to the positive control in this study exhibited average susceptibility of 31 mm for gel 1, 29.67 for gel 2 and 29 for gel 3 against Staphylococcus Aureus and 26.33, 24.67 and 25 for gel 1-3 respectively. This showed opportunity for better susceptibility of niosomes if the dosage strength was increased to higher concentration.

The study also conducted skin irritation testing in order to ensure the safety of the formulation. The gel was applied to 3 albino rabbits compared to mupirocin with a double-blind study approach to avoid bias in the grading. Edema and Erythema were not observed from time 0 till 72 hours.

Controlling the development of short-sightedness in children using atropine loaded contact lenses

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Poster

Background: Myopia or short-sightedness is increasing in prevalence around the world, with the biggest increases in Asian countries. If left unchecked, high levels of myopia can cause blindness. The only known ways of reducing the development of myopia are increasing outdoor activity, using specially designed contact lenses or dosing the eye with atropine. It might be ideal to combine all three, and to this end, this study examines whether atropine can be delivered through contact lenses to the eye.

Objectives: Synthesise a stable inclusion complex of atropine that can be loaded into contact lenses and measure release kinetics.

Methods: An inclusion complex was made using atropine base, a stabiliser and phosphate buffer saline of pH 6.5. The stability of atropine was measured by high performance liquid chromatography. The amount of atropine in each millilitre of the inclusion complex was quantified before and after autoclaving (121°C; 15 min). Etafilcon A contact lens was soaked in the inclusion complex for 24 h to calculate the uptake and release of atropine from the lens. UV-visible spectrophotometry and an electrical balance were used for determining the percentage transmittance (% T) and equilibrium water content (EWC) of contact lens.

Results: The stability study showed that atropine was not degraded up to 67 days. The percentage of atropine remaining after autoclaving the inclusion complex was 81.76 percent. Each etafilcon A contact lens took up 3.21±0.07 µg atropine and nearly all of this atropine, 3.18±0.01 µg, was released from a lens within 4h. The % T was 99.80±0.04 % at 479 nm and EWC 52.74±0.56 % of the atropine-stabiliser

loaded contact lens was not significantly different to normal etafilcon A contact lenses.
Conclusion: The current results indicate that atropine can be incorporated into and released from etafilcon A contact lenses using a stabiliser inclusion complex, without changing the contact lens characteristics.

Influence of lung fluid protein types on in vitro dissolution and absorption of an inhalable drug

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Background: Inhaled drug particles deposit and dissolve in the lung fluid (LF) to get absorbed and show therapeutic effects. To keep things simple, we have defined LF as a thin fluid that lies on the surface of airways from nasal to alveolar region. LF consists of mucus, lipids (surfactants), proteins and organic/inorganic salts. Albumin, transferrin and IgG are the key proteins present in the LF. To the best of our knowledge, the impact of lung fluid protein types on dissolution and absorption of inhaled drug particles has not been explored yet. Therefore, we hypothesize that LF proteins such as albumin, transferrin and IgG affect dissolution and absorption of drugs in the lungs.

Purpose: We aimed to investigate the influence of types of LF proteins such as albumin, transferrin and IgG on in vitro permeation of an inhalable model drug, triamcinolone acetonide (TAA). Here, permeation collectively implies two phenomena namely, dissolution of solid drug and its diffusion through the membrane that corresponds to absorption in the lungs.

Methods: Phosphate buffered saline, polyethylene oxide and proteins such as albumin, transferrin and IgG were used to prepare a series of simulated LFs. Viscosity and surface tension of simulated LFs were measured. Small volume custom-made dissolution apparatus that enables the controlled movement of fluid was used to conduct in vitro permeation experiments in simulated LFs.

Results: Viscosity of simulated LFs containing albumin, transferrin and IgG was in the order; IgG < transferrin < albumin whereas, surface tension showed the order; transferrin > albumin and IgG > albumin. In vitro permeation of TAA was higher in simulated LF containing transferrin than IgG.

Conclusions: LF proteins such as albumin, transferrin and IgG may affect dissolution and absorption of drugs in the lungs.

Evidence-based quality scores for rating drug products

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The quality of drug products in the United States has been a matter of growing concern. Buyers and payers of pharmaceuticals have limited insight into measures of drug-product quality. Therefore, a quality-score system driven by data collection is proposed to differentiate between the qualities of drug products produced by different manufacturers. The quality scores derived using this proposed system would be based upon public regulatory data and independently derived chemical data. A workflow for integrating the system into procurement decisions within health care organizations is also suggested. The implementation of such a quality-score system would benefit health care organizations by including the consideration of the quality of products while also considering price as a part of the drug procurement process. Such a system would also benefit the U.S. healthcare industry by bringing accountability and transparency into the drug supply chain and incentivizing manufacturers to place an increased emphasis on the quality and safety of their drug products.

Microemulsion based intravaginal gel for polycystic ovarian syndrome

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Background: Polycystic ovarian syndrome (PCOS) results in infertility, lack of ovulation, obesity, multiple cysts on ovaries, hirsutism and lack of menstruation. Patients are on the high risk of developing type-2 diabetes mellitus and the prevalence is around 60-70%. Metformin hydrochloride is first line drug in treatment of PCOS and specifically in obese patients it is effective to induce ovulation. Metformin HCl is associated with impaired bioavailability (50–60%), lactic acidosis and frequent oral dosing (500 mg 2–3 times a day) in PCOS that ultimately influence the patient compliance. The maximum daily dose can be upto 2500–2550 mg/day. Metformin has dose dependent side effects such as gastrointestinal symptoms of nausea, diarrhea, bloating, anorexia, abdominal pain etc.

Purpose: The purpose of the present investigation was to develop and evaluate microemulsion based gel for intravaginal delivery of Metformin HCl to treat polycystic ovary syndrome.

Method: Initially solubility of Metformin HCl was determined in various oils, surfactants and co-surfactants to identify the maximum area of microemulsion.

Microemulsion formulations were prepared by water titration method and evaluated for particle size and zeta potential. Thermosensitive gelling agents were evaluated for their potential to gel metformin microemulsion without affecting its structure. The prepared formulation of Metformin HCl microemulsion based gel was evaluated for physicochemical properties.

Results: Based on pseudoternary phase diagrams Metformin HCl showed high microemulsion zone using soluble in lavender oil, Ykang Ylang oil, Thyme oil, eucalyptus oil and clary sage oil as oil phase Tween 60 as surfactant and ethanol as co surfactant. Formulation F1 consisting of Smix ratio of 9:1 (Lavender oil: tween 60: ethanol) showed more than 90% of drug diffusion and similarly for Ex vivo studies conducted on sheep vaginal mucosa also showed drug diffusion of around 91.35%. This may be due to the fact that these oils also improves permeation of drugs through the biological membranes. The mean particle size and zeta-potential of optimized Metformin HCl microemulsions (F1) were measured to be in the range of 798 nm to 806 nm and -38.01 to - 40.24 mV, respectively. The combined effect of essential oils and particle size of microemulsions might have contributed to better diffusion of drug through mucosal membrane. Polydipersity Index was observed to be in the range of 0.88 to 0.702 which is within the range of homogeneity. Bioadhesion and long retention are desirable characteristics of a vaginal formulation. Poloxomer acts as thermogelling mucoadhesive polymer. Performed adhesion force studies and retention studies proves that the microemulsion based vaginal gel formulation exhibits good retention time.

Conclusion: The developed thermosensitive intravaginal gel has good potential to treat poly cystic ovarian syndrome. Intravaginal gels can deliver drug directly into the systemic circulation by passing hepatic first pass effect, hence the dose dependent side effect caused due to oral administration caused due to metformin hydrochloride can be reduced. The developed delivery system would help to reduce the dosing frequency and being noninvasive greatly improves patient compliance.

Developing advanced lipid-based oral delivery formulations for treating luekemia

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Background: Acute myeloid luekemia (AML) is an aggressive haematological malignancy which represents a major unmet medical need due to current sub-optimal treatment approaches. Venetoclax is an orally administered BCS Class IV used for the treatment of various forms of leukeamia and lymphoma. Its low solubility and permeability alongside its pharmaceutical food effect presents a sub-optimal pharmacokinetic profile impacting oral bioavailability. Reformulation of cancer therapeutics into nanocarriers can improve their stability and biopharmaceutical performance, and ultimately lead to enhanced treatment outcomes.

Objective: The objective of this work is to investigate the development of lipid-based drug delivery systems (LBDDS) as a novel bio-enabling approach to overcome oral delivery challenges of Venetoclax.

Methods: A literature review was essential to identify proof-of-concept studies of LBDDS for the oral delivery of challenging anti-cancer agents. Biorelevant solubility of pure Venetoclax was determined in fasted and fed-state simulating intestinal fluid (FaSSIF & FeSSIF) using a pH-stat titration apparatus. Literature findings enabled smart selection of excipients, whereby solubility of the drug in various oils (Peceol, Capmul MCM etc.), surfactants (Tween, Pluronic, Poloxamer) and co-surfactants in addition to surfactant screening via emulsification studies were conducted. Solubility studies were also conducted at higher temperatures of 40 °C and 60 °C to determine the effect of supersaturation on drug loading.

Results: Various LBDDS (self-emulsifying drug delivery systems, solid lipid nanoparticles, nanostructured lipid carriers) have shown success in the literature for enhancing oral drug, reducing toxicity profile and enabling co-delivery for synergistic effect for a range of anti-cancer agents. Venetoclax displayed a significant increase in solubility between fasted and fed states, confirming the pharmaceutical food effect it exhibits and confirms the use of lipid formulation to mitigate the food effect. Peceol, Tween 85 and Cremophor RH40 displayed desirable solubility and emulsification ability, with supersatured Peceol exhibiting greater drug loading.

Conclusions: The review demonstrated that the type of LBDDS, its corresponding properties and treatment strategy (single or combination therapy) are critical factors to consider when developing lipid-based oral delivery formulations. This project will explore the hypothesis that the performance of anti-leukemic agents can be enhanced by encapsulating Venetoclax as a model compound into a lipid nanoparticle system, as a single and co-delivery with other anti-leukemic agents. Formulation preparation of a self-emulsifying drug delivery system and subsequent characterisation will occur.

Bioresorbable delayed release implant for livestock immunisation

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Background: Ensuring appropriate disease prevention of Australian livestock is of utmost importance to maintain industry viability. Vaccinations against several diseases in sheep and cattle are common practice and typically involve the administration of primary and booster immunisations. Re-herding of livestock at least four to six weeks after the initial dose places significant logistical burdens on personnel to ensure all animals receive the required doses. A single administration of both initial and booster doses may be achieved using bioresorbable implants to allow delayed release of the booster dose based on the degradation of the polymer. This reservoir-style implantable device also allows minimal payload handling during manufacture and eliminates the need to remove the implant once the payload has been released by using a bioresorbable polymer.

Purpose: This study aims to understand the relationship between the composition of a bioresorbable terpolymer implant and its capacity to enable the delayed release of a model payload.

Method: Thin-walled tubes were fabricated by dip-coating into a 12% w/v terpolymer solution dissolved in hexafluoro-2-propanol. The terpolymer is composed of glycolide, trimethylene carbonate and caprolactone. Following an annealing process, implants were cut to size, and filled with blue food dye as a model payload, then sealed. Loaded implants were placed in PBS and incubated at 37°C and 55°C (accelerated degradation). Payload-free implants were used for additional characterisation assays including, mass and pH change, thermal and mechanical analysis, and imaging.

Results: A delayed release profile was observed from the implant using this terpolymer composition. The accelerated assay at 55°C allowed efficient initial screening of the implant release profile due to the long lag time. Superposition of the accelerated assay with release data at 37°C showed a good correlation, indicating release occurred from 38 days, followed by sustained release over 30 days. A minimal terpolymer mass change of 4.3 % was observed for the first 28 days, before an overall decrease of 14.9 % by 42 days. An acidic pH of 3.16 and change in glass transition from -20.6°C to -37.9°C and melting temperatures from 203.6°C to 188.1°C by 42 days supports degradation of the terpolymer via chain scission by a combination of bulk and surface erosion. The surface morphology by scanning electron microscopy revealed pitting of the implant over time, congruent with surface erosion and further micro-CT analysis did not indicate visible porosity or defects through the implant wall.

Conclusion: The delayed release profile attained from this terpolymer provides a promising outlook on the role of alternative polyester-based devices for controlled drug delivery. These results suggest diffusion could be the prominent mechanism facilitating delayed release of the payload, once the terpolymer reaches a particular physicochemical state. It is known from literature that payload properties may play another influential role, therefore release kinetics and stability of a relevant vaccine payload will be investigated in future work.

Novelty of quantum dots as a drug delivery vehicle design for nanoparticle

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Introduction: Quantum dots (QDs) due to their unique physicochemical characteristics are regarded as efficient fluorescent markers utilized in a drug delivery system for monitoring the metabolic process of drugs in the body. They can also be employed in a variety of biomedical applications, like fluorescence assays for disease diagnosis and drug development.

Objective: This study aims to conduct a review of the Quantum dots as a platform for nanoparticle drug delivery vehicle design.

Method: Electronic databases were searched from inception for articles published in English and examining the use of quantum dots as a framework for the development of nanoparticle drug delivery vehicles. The database included were MEDLINE, EMBASE, and Psych INFO. Information was systematically extracted, analyzed, and discussed.

Results: Although 52 papers were found, the study only included 10 that met the inclusion criteria. This research made me able to show that, among the several contrast agents available for researching Nanoparticle-based drug delivery (NDD) vehicles, quantum dots (QDots) are particularly well suited. quantum dots (QDots) are an attractive platform for the complete study of Nanoparticle-based drug delivery (NDD) vehicle behavior across single-cell to whole-organism levels because of their unique combination of relevant qualities, such as tiny size, variable surface chemistry, and exquisite optical properties.

Conclusion: quantum dot's compactness and dynamic surface chemistry enable them to be incorporated into virtually any Nanoparticle-based drug delivery (NDD) vehicle

with negligible impact on overall attributes, and they have excellent optical characteristics for real-time monitoring of Nanoparticle-based drug delivery (NDD) vehicle transport and drug release at both the cellular and systemic levels. However, more research is needed to tackle the most difficult diseases, which is still the most uncharted but intriguing field for quantum dots (QDots).

Atractylodes lancea Rhizome-derived exosome-like nanoparticles suppress lipopolysaccharide-induced inflammation by murine microglial cells

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Background: Exosome-like nanoparticles (ELNs) have interspecies intercellular communication and modulate gene expression.

Purpose: The purpose of this study was to evaluate the potential of Atractylodes lancea rhizome-derived ELNs (ALR-ELNs) as a neuroinflammatory therapeutic agent.

Method: We isolated and purified ELNs from dried rhizome of ALR-ELNs, which is a traditional natural medicine. First, we identified and characterized ALR-ELNs as a new compound that can affect the BV2 microglial response to LPS and modulate the expression of genes involved in the inflammatory response, cytokine release, and oxidative stress. Additionally, by combining data from a publicly available library of miRNAs and data on the ALR-ELN cargo, we aimed to identify candidate mRNA targets.

Results: ALR-ELN pretreatment of BV2 cells prevented the pro-inflammatory effects of LPS stimulation by significantly reducing the levels of NO, IL-1β, IL-6, and TNF-α. Additionally, while mRNA expressions of iNos, Il1b, Il6, and Tnfa increased in BV2 cells upon LPS treatment, they significantly reduced following ALR-ELN treatment. Moreover, BV2 cell expression of heme oxygenase 1 rRNA significantly increased following ALR-ELN treatment. BV-2 cells were found to internalize ALR-ELNs, which comprised three micro RNAs (i.e., ath-miR166f, ath-miR162a-5p, and ath-miR162b-5p) that may be involved in anti-inflammatory processes.

Conclusion: Our study indicates that ALR-ELNs can be considered candidate therapeutic carriers of bioactive compounds that may potentially modulate neuroinflammatory disorders.

Optimization of the ultrasound-assisted extraction process for the purification of phosphatidylcholine from rice bran lecithin using Box-Behnken response surface methodology and analysis of rice bran phosphatidylcholine emulsifying property

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Background: Phosphatidylcholine (PC), a pharmaceutical excipient, is employed in a variety of formulations, including fat emulsions and liposomal preparations. It functions as an emulsifier and liposome former. The type and purity of PC significantly impact the quality of products. Most natural PC used in pharmaceutical formulations is purified from soybean lecithin and egg yolk using non-toxic solvent extraction. Among natural sources, rice bran lecithin (RBL) is an attractive material due to its high PC content; nevertheless, rice bran PC has not yet been commercially available, despite various methods being used to extract and purify it. Ultrasound-assisted extraction (UAE) is an alternative technique that can be applied for rice bran PC purification. Box-Behnken design (BBD) has been employed to prepare the experimental plan for improving rice bran PC purity.

Purpose: The aim of this study was to optimize the UAE process for enhancing the purity of rice bran PC using the BBD and evaluate its emulsifying properties for usage in pharmaceutical applications.

Method: The UAE process for the PC purification of rice bran lecithin was performed using an ultrasonic bath. A three-level, four-factor BBD was employed to determine the optimal condition of the UAE process. The tested factors were the ratio of RBL to solvent (1:5, 1:7, and 1:9 w/v), the percentage of water in the solvent (0, 2, and 4% v/v), the temperature of the UAE (40, 55, and 70 ^{o}C), and the time of the UAE (30, 60, and 90 min). All samples obtained from the UAE process were calculated for yield (% w/w) and subsequently characterized using high-performance thin-layer chromatography (HPTLC) to determine the purity of PC. The emulsifying capacity of rice bran PC was investigated in a mixture of rice bran oil and water and compared with that of soybean PC. The rheology and creaming index of the obtained emulsion were evaluated.

Results: The Box-Behnken method had generated 26 experimental runs. All factors of the UAE process significantly ($P \leq 0.05$) affected the yield and purity of rice bran PC. A quadratic polynomial model was determined to be suitable for prediction of the optimal UAE process. The regression coefficient ($R^2 = 0.9495$), the lack-of-fit test ($P \geq 0.05$), and the signal-to-noise ratio (11.17) indicated good accuracy and an adequate signal of the derived model. The highest purity of rice bran PC predicted from the model was 65.22% using a 1:7.4 RBL to solvent ratio, 1.2% water in the

solvent, 62 °C, and 90 minutes of ultrasonic time. For the experimental samples, their HPTLC fingerprints qualitatively revealed a predominant amount of PC. The highest PC purity was 63.08%, which is comparable with the predicted value. Both rice bran PC and soybean PC-based emulsions exhibited non-Newtonian pseudoplastic behavior. Rice bran PC-based emulsion displayed better stability than soybean PC-based emulsion, with a creaming index of 39.63% and 50.88%, respectively.

Conclusion: The optimized UAE process from the Box-Behnken design could maximize the purity of rice bran PC. The rice bran PC could be used as an emulsifier.

Impact of different apolipoprotein E isoforms on the in-vitro expression and function of P-glycoprotein at the blood-brain barrier

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Background: Alzheimer's disease (AD) is a neurodegenerative condition which manifests in progressive cognitive decline. Individuals often take multiple medications, both for AD and other comorbidities, and these medications are dosed in a manner irrespective of whether or not an individual has AD. This is despite knowledge that pathological alterations occur in AD, including blood-brain barrier (BBB) disruption such as the downregulation of P-glycoprotein (P-gp), a key efflux transporter that prevents central nervous system entry of many drug substrates. The apolipoprotein E (apoE) gene, which has three human protein isoforms; apoE2, apoE3 and apoE4, has the strongest genetic link in the development of sporadic AD. ApoE3 is the most abundant isoform, whereas apoE4 confers an increased risk of AD. The effect that apoE isoforms play on drug transporter expression and function at the BBB is not well known, albeit there is growing evidence showing apoE status impacts general BBB permeability.

Purpose: To investigate the impact of different apoE isoforms on P-gp expression and function in human brain microvascular endothelial cells (hCMEC/D3 cells).

Method: Recombinant apoE3 and apoE4 were administered to cultured hCMEC/D3 cells, an in-vitro model of the BBB, at a concentration of 2 µg/mL for a period of 24, 48 and 72 hours. SR12813, a compound known to increase P-gp expression, was utilised as a positive control for a period of 72 hours. Following treatment, P-gp protein expression was assessed via Western blot. P-gp function was assessed after a 48 hour treatment via the accumulation of rhodamine 123 (R123), a fluorescent P-gp substrate.

Results: P-gp expression in hCMEC/D3 cells was not altered with the treatment of recombinant apoE4 relative to recombinant apoE3 for the 24-72 hour timepoints investigated. P-gp function via R123 accumulation was also unchanged after a 48 hour treatment. SR12813 significantly increased P-gp expression approximately 1.36-fold, indicating P-gp protein expression is modifiable in the in-vitro system.

Conclusion: Our results suggest that the difference in apoE isoforms has no direct influence on P-gp expression or function at the concentration investigated, potentially due to the acute nature of the study design and inherent limitations of the in-vitro system. Future studies utilising a targeted-replacement mouse model expressing humanised apoE isoforms are planned to determine potential changes within an intact biological system.

Assessing the in vitro dissolution rate of metformin from different commercially available tablets using distinct physiological pH media at different fast/fed states

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Background and objective: Metformin is a common and effective medicine used worldwide to increase insulin secretion levels from the pancreas and enhance the sensitivity of the insulin receptors1. According to the Food and Drug Administration (FDA), regulations different generics must have similar levels of bioavailability after ingestion, which will depend indirectly on the dissolution rate of the medicine and subsequent absorption levels2. There is a need to investigate and compare the dissolution rate between different brands of metformin, which can be affected by the pH and the viscosity of the physiological media3,4. The objective of this study is to compare between the in vitro dissolution of different generics of metformin Immediate Release (IR) and Extended Release (ER) tablets at different pH and using different dissolution media simulating the fast/fed state of the stomach in the gastrointestinal tract.

Methods: Preparation of media with different viscosities will be completed by using different concentrations of HPMC and thickened water (with different viscosities) using a viscometer. Assessing the in vitro dissolution of metformin over time from different brands of metformin tablets will be conducted using the USP method II of a Distek dissolution apparatus.

Results: The metformin XR tablets showed a slow release of metformin compared with the drug from IR tablets (96% at 10 min in IR tablets compared to 76% after 5 hours for XR tablets of in vitro dissolution in phosphate buffer at pH=6.8). Results showed a difference of metformin released after 5 hours of in vitro dissolution in phosphate buffer at pH=6.8 for the different brands of XR metformin brands. The in vitro dissolution of metformin in an acidic pH was very slow compared to the one in phosphate buffer at pH=6.8. Results indicated a difference in the in vitro dissolution of metformin from XR tablets in media with different viscosities.

Conclusion: Variation in the vitro dissolution of different brands of metformin XR tablets or in the different media pH or viscosity may suggest difference in the bioavailability of the tablets in vivo.

Impact of vinification techniques on antioxidant activity of fermented grape pomace

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Background: Grape pomace is an inexpensive source for the extraction of phenolic compounds that can be used in the pharmaceutical and food industries. Phenolic compounds are secondary plant metabolites with beneficial effects on human health because of their antioxidant properties. It is necessary to have efficient extraction techniques to achieve good recoveries of these compounds from grape pomace.

Purpose: The aim of this study was to evaluate antioxidant activity of fermented pomace obtained after classic maceration and thermomaceration of red grapes.

Methods: In terms of wine production three different experiments were conducted. The first experiment was control sample and classic maceration was applied for a period of 14 days. The maceration of other two experiments lasted also 14 days but before that samples were subjected to prefermentative heating of grape solids (60℃, 60 min and 80℃, 30 min). A commercial yeast BDX (Lallemand, Canada) was inoculated in all of samples. After maceration, fermented pomace was separated from wine and stored until analyses. It was followed by lyophilization of fermented pomace and optimized extraction with methanol and deionized water. Antioxidant activity by FRAP method and TEAC test were evaluated in obtained pomace extracts and expressed as µmol/g of lyophilised pomace.

Results: The pomace sample, which exposed to higher temperature treatment, showed the highest antioxidant activity measured by FRAP method and TEAC test (286,5 µmol Fe2+/g of lyophilised pomace and 149.9 µmol TE/ g of lyophilised pomace, respectively).

Conclusion: The results showed that fermented pomace which retained after thermomaceration had a higher antioxidant activity compared with classic macerated pomace.

Preclinical development of an injectable Multipurpose Prevention Technology (MPT) formulation for contraception and HIV prevention

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Background: There is growing interest in the development of MPT products for women that combine hormonal contraception with HIV prevention. Since long-acting injectable (LAI) contraceptive products are already widely used by women in countries where HIV infection is highest, and efforts are ongoing to develop injectable antiretroviral formulations, there is strong rationale for combining a progestin and antiretroviral drug in a single injectable product.

Purpose: Here, we report preclincial development of a LAI aqueous suspension product containing the antiretroviral rilpivirine (RPV) and the progestin medroxyprogesterone acetate (MPA).

Method: RPV was milled to produce an aqueous nanosuspension, and then reformulated with the commercial micronised Depot MPA (DMPA) to produce the MPT test product (~90mg/mL RPV; ~45mg/mL MPA). Suspension formulations were characterized for particle size, charge, pH, osmolality, drug concentration, and by thermal analysis. The lead candidate MPT formulation, a commercial DMPA product, and a RPV-only nanosuspension were administered intramuscularly in cynomolgus monkeys for 90-day pharmacokinetic evaluation, with quantification of MPA/RPV in vaginal fluid/blood plasma by UPLC-MS/MS.

Results: All test formulations were confirmed sterile and stable over three months, and the separate agents had the following Dv(50) values: RPV ~114 nm; MPA ~ 10.6 µm. Plasma concentrations of RPV and MPA in macaques decreased from ~100 ng/mL to ~0.1 ng/mL, and over time periods ranging from 25–70 days depending upon the formulation. RPV vaginal fluid concentrations decreased from ~100 ng/g to ~2 ng/g over up to 40 days.

Conclusion: This study demonstrates the potential for reformulating DMPA with an antiretrovral drug as a LAI MPT strategy for contraception and HIV prevention. Further work is needed to maintain drug concentrations over longer periods of time.

Characterization and evaluation of tablets prepared from different native starches

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Background: Starch, the most abundant carbohydrate molecule found in tropical plants, is a staple food but can be used as excipients in pharmaceutical preparations. In the pharmaceutical industry, maize and potato starches are often used as a binder and disintegrants in the tablet formulation.
Purpose: In the present work, the physicochemical properties and disintegration capability of isolated native starches from kernels of litchi and mango, were tested and further the tablets of these starches were prepared and evaluated.

Material and method: Tablets containing paracetamol as a model drug, were prepared by the wet granulation method using different varieties of isolated native starches. Based on the compendial specifications, the physical, chemical, disintegrant properties, and dissolution profiles of the isolated starches were measured and evaluated.

Results: Isolated native starches possess satisfactory values of different parameters such as amylose content (< 25.31 ± 0.4), solubility (< 25.38 ± 0.3 %), swelling power (< 19.07 ± 0.4 g/g), and water absorption capacity (< 102.51 ± 0.8 %). Furthermore, all tablets with different starches showed acceptable average tablet weight variation, hardness (> 4 kg), friability (< 1 %), and disintegration time (< 15 min). The tablets passed the dissolution test for immediate-release tablets (≥ 70 % release in 15 min).

Conclusion: Isolated native starches passed the starch's physicochemical tests, including tablet quality control tests, and can be used as an alternative source of starch in the pharmaceutical industry.

An inhalable hybrid biomimetic nanoplatform for on-demand drug release and modulating lung microenvironment in acute lung injury treatment

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Background: Lung inflammation initiated by proinflammatory macrophages and neutrophils is responsible for high morbidity and mortality during acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Either directly inhibiting macrophage over-activation states or destroying neutrophils cannot guarantee a satisfactory long-term effect in survivors of ARDS.

Purpose: Herein, we showed that the coordinated action of neutrophils and lung macrophages was disturbed by inhalation of methylprednisolone (MPS) loaded enzyme-responsive nanoplatforms (termed D-SELs) composed of serum exosomal and liposomal hybrid nanocarriers (termed SELs) covered with cleavable DNase I arms.

Method: To pursue maximized synergistic efficacy in LPS induced acute lung injury (ALI) mice, MPS and DNase I was successfully formulated to be physically encapsulated and chemically conjugated into SELs, respectively. First, MPS/liposome was fused with serum exosome with freeze-thaw method. The DNase Ⅰ – MMP 9 cleavable peptide was then conjugated to the surface of SEL (termed as D-SEL) using copper-free click chemistry to establish an inhalable inflamed alveoli microenvironment enzyme-responsive nanoplatform.

Results: In lipopolysaccharide (LPS) induced ALI mice, inhalation of MPS/D-SEL displayed efficient permeation through airway mucus barrier and prolonged lung retention time with the aid of mucolytic arms. Additionally, DNase I was released from the nanocarrier first after responding to matrix metalloprotease 9, resulting in inner MPS/SEL core exposing, which realized precise macrophages-targeted delivery of MPS for directly modulating macrophage polarization into M2 phenotype. Sustained release of DNase I promoted dysregulated neutrophil extracellular traps (NETs) degradation and mucus plugging microenvironment inhibition, which in turn amplified M2 macrophage polarization efficiency. Such on-demand release behavior successfully interrupted the crosstalk between neutrophils and lung macrophages, suppressed hyper-inflammatory lung microenvironment, leading to damaged lung tissues restoration.

Conclusion: This work presents a versatile hybrid biomimetic nanoplatform for the locally pulmonary delivery of dual-drug therapeutics and displays potential in the treatment of acute lung inflammatory diseases.

Injectable microparticle for the sustained release of Aripiprazole: formulation design and pharmacokinetic assessment

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Background: Aripiprazole (APZ) is commonly prescribed as an antipsychotic drug for patients with schizophrenia. While sustained APZ injections are available for the management of schizophrenia, current treatment regimens also call for oral APZ for 14 to 21 days following the initial injection due to the drug's poor solubility. To reduce the frequency of co-administration of oral tablets and overcome patient medication adherence, a practical and efficient sustained formulation is required.

Purpose: The aim of this study is to combine immediate-release and extended-release formulations to develop a once-monthly APZ injection without the requirement of co-administration of oral tablets. Therapeutic APZ concentrations is expected to reach rapidly when treatment first begins.

Method: Aripiprazole was prepared as micro-suspension by combined bottom-up and top-down approach based on acid-base neutralization. The formulation is composed of acidifier 1N HCl and co-solvents methylcellulose (HPMC) or polyvinylpyrrolidone (PVP), and the effect of different ratios on the solubility of APZ was tested. To discover suitable formulations, the in vitro dissolution test and a range of physical property evaluations were performed. The ideal formulations are selected for in vivo pharmacokinetics tests at a dose of 50 mg/kg for 43 days using Sprague Dawley rats.

Results: The results of X-ray powder diffraction analysis, differential scanning calorimetry and Fourier transform infrared spectroscopy demonstrated that the formulations of HPMC or PVP 150 mg with 1N HCl 52 or 103 µL (H150-52, H150-103, P150-52 and P150-103) had a similar crystal structure to Abilify MAINTENA® (Commercial products) after the microprecipitation/homogenization processes. It was observed that the increase of co-solvent content could reduce the particle size and exhibit a rapid release of the drug. In addition, 150 mg HPMC or PVP with 103 µL 1N HCl (H150-103, P150-103) increased the solubility of APZ products by about 2 times, and 150 mg HPMC or PVP with 52 µL 1N HCl (H150-52, P150-52) increased the solubility of APZ products by about 1.22 times and 1.36 times, respectively.
Pharmacokinetic tests revealed that the AUC0-10 of the HPMC group at a dose of 50 mg/kg was higher than that of the APZ product. It showed a greater Cmax and a similar T1/2 when compared to commercial oral products, indicating that the oral administration is not the necessity or the number of tablets taken can be reduced. Additionally, the therapeutic drug concentration can be attained immediately and last up to one month.

Conclusion: This research serves as a proof-of-concept for the use of acid-base neutralization-based micro-precipitation/homogenization to develop stable injectable micro-suspensions that combine instant and sustained drug release. Future work will be focused on enhancing pharmacokinetics and in vivo safety as well as researching potential application of this technique in different diseases to address medication compliance.

Development of abemaciclib-loaded solid lipid nanoparticles using quality-by-design approach and evaluation of its anticancer activity in MDA-MB-231 and T47D breast cancer cells

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Background: Abemaciclib (ABE) is an anticancer drug approved by the United States Food and Drug Administration that inhibits the activity of cyclin-dependent kinases 4 and 6 in advanced or metastatic breast cancer. However, low bioavailability and multidrug resistance are the major drawbacks to its effective use.

Purpose: In this study, we have developed ABE-loaded solid lipid nanoparticles (ABE-SLNs) by enhancing ABE solubility to improve its cytotoxicity and cellular uptake.

Methods: The ABE-SLNs were optimised using the Quality-by-Design approach and characterised for particle size, polydispersity index, zeta potential, and entrapment efficiency. Further anticancer effectiveness of the optimized formulation was studied against MDA-MB-231 and T47D breast cancer cell lines.

Results: ABE-SLNs were prepared using Precirol® ATO5 lipid and stabilised by Brij-58. The particle size of the optimised formulation was 170.4 ± 0.49 nm, and the PDI value was 0.25± 0.014. The zeta potential measured was -26.4 ± 0.1 mV, and the ABE-SLN demonstrated a high entrapment efficiency of 79.96% with sustained-release behaviour. ABE-SLNs showed higher anticancer activity in MDA-MB-231 and T47D breast cancer cell lines and enhanced internalisation compared to pure drugs. Furthermore, ABE-SLNs showed enhanced cellular uptake in Caco-2 human colonic cell lines.

Conclusion: This study suggests that optimised ABE-SLNs may be a potential nanocarrier to achieve sustained release and enhanced cellular uptake.

Evaluation of the cytotoxic effect and wound healing property of chrysin and its incorporation in nanofiber mat

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Background: Numerous studies have highlighted the potential of natural compounds for the treatment of wounds, particularly those with antimicrobial, antioxidant, and anti-inflammatory properties. Chrysin, a naturally occurring flavonoid with anti-inflammatory properties, has recently been studied for its ability to promote wound healing. However, chrysin cannot be used as a drug to treat wounds due to its poor water solubility. Electrospun nanofiber mat, an advanced wound dressing material, can provide a solution for improving the drug's solubility due to the high surface area of the nanofibers, and their hydrophilic property further enhances the drug dissolution rate. The chrysin limitation is anticipated to be solved by incorporating chrysin into a nanofiber mat prepared from hydrophilic polymers such as chitosan (CS) and polyvinyl alcohol (PVA). Still, more information is needed about the cytotoxic effect and wound healing property of chrysin combined with these polymers in order to prepare a chrysin-loaded CS/PVA nanofiber mat.

Purpose: The main aim of the study was to investigate the cytotoxic effect and wound healing properties of chrysin and CS/PVA solutions and the subsequent incorporation of chrysin into a CS/PVA nanofiber mat.

Methods: The effects of chrysin, CS/PVA solution, and chrysin combined with CS/PVA solution on the toxicity of the human keratinocyte (HaCaT) cell line were evaluated using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, and their ability to heal wounds was investigated in vitro utilizing the scratch assay. Chrysin-loaded CS/PVA nanofiber mat was prepared by an electrospinning process. The morphology of the nanofiber mat was observed under a scanning electron microscope (SEM) to confirm the incorporation of chrysin into the nanofibers. Its diameter was measured from the SEM image.

Results: The results from the MTT assay revealed that chrysin (5-75 µg/ml) exhibited a concentration- and time-dependent decrease in cell viability, with an IC50 value of 43.25±0.17 µg/ml after 24 hours of treatment, while the CS/PVA solution showed no toxic effect on HaCaT cells. The combination of chrysin and CS/PVA solution exhibited a similar cell viability profile as that of chrysin, with the IC50 value increasing to 76.91±1.38 µg/ml. However, the viability of cells treated with 10 µg/ml of chrysin alone or combined with a CS/PVA solution was greater than 80%. Therefore, this concentration was selected for the wound healing study. Chrysin combined with CS/PVA solution significantly promoted cell migration into the wound area, with 3.20 and 2.42-fold higher wound closure than chrysin and CS/PVA solution, respectively. Chrysin was electrospun and completely incorporated into the CS/PVA nanofiber mat. The SEM image indicated that the bead-free nanofibers were obtained without chrysin crystals. The diameter of chrysin-loaded CS/PVA nanofibers was in the range of 180-290 nanometers.

Conclusion: Chrysin accelerated cell migration and exerted a synergistic effect with the CS/PVA solution on wound closure without toxicity at low concentrations. Chrysin-loaded CS/PVA nanofiber mat was successfully prepared using the electrospinning process.

Unlocking the potential of cannabidiol: Preliminary findings on the benefits of a phospholipid complex

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Background: Cannabidiol (CBD) has shown potential for several medical conditions, including the treatment of epilepsy, multiple sclerosis, Alzheimer's, Parkinson's, and Crohn's diseases [1]. While there is growing investigation for its prospective use as an analgesic, anti-inflammatory, antitumor, antidepressant, and anxiolytic effects [2], the full potential use of oral CBD is hindered by its poor water solubility (0.7 - 10 µg/mL), low permeability, and chemical instability [3]. Phospholipid (PL) complexes are biodegradable and nontoxic vesicles that can act as a powerful delivery system for CBD [4].

Purpose: The aim of this study was to screen PL and optimize the ratio between CBD and the selected PL using the Design of Experiments (DOE).

Method: The complex was prepared by the thin film hydration method. This method involves dissolving the desired PL and CBD in ethanol and then evaporating the solvent under reduced pressure to form a thin film. The film is then hydrated with an aqueous solution to form liposomes. The preliminary investigation compared the effects of four PLs on the water solubility, particle size, and Polydispersity Index (PDI). Dynamic light scattering technique was used to determine the effect of CBD-PL on droplet size in different pH levels and PDI. Octanol-water partition coefficient (Po/w) of pure CBD, CBD-PL, and physical mixture were measured by adding the samples to water solutions at different pH values, agitating them, and separating the water and n-octanol phases for analysis using the HPLC system. The response surface methodology (RSM) predicted the best ratio between CBD and the selected PL.

Results: The study on solubility revealed that PC-98T demonstrated superior outcomes. The particle size and PDI analysis showed that encapsulation of CBD with PC-98T resulted in smaller particles with more consistent sizes across different pH levels. The optimum formulation

predicted by DOE exhibited a droplet size of 145 nm and a PDI value of 0.266. The Po/w value for the predicted CBD-PL by DOE was 0.0066±0.004 in PBS 7.4. No recovery of CBD in water solutions was shown for the pure drug. For the physical mixture in PBS 1.2 and 4.5, the Po/w values were 0.0013±0.0018 and 0.0019±0.0027, respectively. No recovery was seen for the physical mixture in PBS 7.4. The release profile of CBD was slow, as expected for the complex.

Conclusion: The study demonstrated that encapsulation of CBD with PC-98T improved water solubility and led to smaller particle size, and the size distribution is highly homogeneous. Additionally, the optimum formulation had a substantial Po/w, demonstrating improvement in the aqueous solubility of CBD. These findings highlight the potential of liposomes as a delivery system for CBD and may have important implications for the development of CBD-based therapies for various medical conditions.

A shot at a better life: Long-acting injectable for Parkinson's disease

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Background: Parkinson's disease is a debilitating neurodegenerative disorder. Conventional therapies are available for Parkinson's disease are associated with limitations such as the wearing-off effect, on-off period, episodes of motor freezing, and dyskinesia. Reports suggest that such side effects are mainly due to the fluctuation in the plasma concentration of the drugs, which necessitates multiple doses for attending the therapeutic concentration. The available marketed formulations include oral tablets and capsules, which require multiple-time administration due to the short half-life and extensive metabolism of the drug after oral administration, which becomes inconvenient to older patients. We aim to prepare a sustain-release parenteral formulation of levodopa and carbidopa, a gold-standard treatment for Parkinson's disease.

Purpose: Our current hypothesis is to develop a long-acting injectable oleogel for Parkinson's disease which will release the drug for a longer time (7 days) avoiding fluctuations in plasma concentration and reducing the dosing frequency of levodopa. Oleogels have been successfully used to obtain sustained drug release for hydrophilic and lipophilic drugs.

Method: Oleogel formulations were prepared by heating beeswax or ethyl cellulose (2-10% concentration) in miglyol 812 until it completely solubilizes in it. Drugs were added once the temperature comes down to 40°C to avoid the degradation of drugs. Oleogel formulations were stirred until a uniform dispersion was formed. Once cool down all the formulations will be characterized for in-vitro drug release, DSC, FTIR, SEM, content uniformity, and syringe ability. Due to the instability of levodopa and carbidopa in release media (pH 7.4), discoloration of the release samples was observed.

Results: To prevent the degradation of drugs in release media, we evaluated the stability of both the drugs in presence of different antioxidants (EDTA, Ascorbic acid, Sodium bisulfite, and butylated hydroxytoluene. Amongst the evaluated antioxidants sodium bisulfite at 0.1% concentration prevented degradation. Further in-vitro release studies will be performed for all the formulations for 7days.

Conclusion: The development of a sustained-release injectable oleogel formulation of levodopa and carbidopa for the management of Parkinson's disease has the potential to overcome the limitations associated with conventional therapies, such as the need for frequent dosing and side effects. The addition of sodium bisulfite as an antioxidant showed promising results for preventing the degradation of the drugs in the release media.

Reviewing the effects of monoclonal antibody formulations, with relevance to rheumatoid arthritis

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Introduction: Monoclonal antibodies (mAbs) are a class of biological therapeutic agents used in Oncology or autoimmune diseases like Rheumatoid arthritis (RA). Its sensitivity in ambient conditions causes instability during manufacturing, storage and administration. Employing certain conditions and excipients may improve the mAbs' pharmaceutical stability. The mAb market is projected to be worth approximately US$425 billion by 2028 and is driven by innovation in drug design and development. Optimising mAbs also paves the way for successful outreach of biosimilars, another valuable aspect of the pharmaceutical industry, to consumers. Thus, reinforcing the need for continued optimisation of mAb formulations for improved efficacy and favourable adverse effect profiles.

Aim: To critically analyse the effectiveness and suitability of common (amino acids, silicone oil) and novel (dipicolinic acid, quinolinic acid, arginine-glutamate) excipients in overcoming challenges faced by mAb formulations such as viscosity, opalescence and aggregation. Concomitantly, formulation optimisation, with respect to present findings and factors such as storage, technology, manufacturing and stress conditions have also been explored in detail.

Methods: 2 trial types were selected using PRISMA Guidelines. Adopting a highly specific inclusion and exclusion criteria, the first type is associated with excipients and their effects on protein stability whereas the second was clinical trials, where the safety and efficacy of mAbs used in RA were demonstrated. A tocilizumab trial was selected to demonstrate its safety and efficacy of in RA, and the major

findings of the other trials regarding the excipients were adapted to the findings of this trial.

Results: Amino acids have concentration dependent stabilising and de-stabilising effects whereas silicone oil induces aggregation and protein instability, affecting conformational stability. Arginine-Glutamate has shown promise alongside Arginine-Quinolinic acid, as an opalescence and viscosity modifier. Agitation and stress induced the most aggregation, leading to colloidal instability. Based on the results, the tocilizumab formulation was deemed as suitable as otherwise, issues such as hypersensitivity, anaphylaxis and poor compliance would have been reported.

Conclusion: Further research is required in the area of arginine complexes to strengthen their suitability as excipients. However, it is noteworthy that even if a formulation remains stable in vitro, it may change due to patient variability in vivo. There is a lack of head-to -head trials that compare the safety and efficacy of biologics used in RA. The available clinical data however, shows variability in patient response to these agents, reinforcing the need for more reliable clinical markers, which should be addressed by the formulation and licensing of new agents. In turn, this creates more potential for research to be conducted in terms of formulation optimisation as well as evaluating mAb therapeutics in different patient types. Nonetheless, the progress for biologic optimisation so far looks promising.

PharmBCS: A Biopharmaceutical Classification System (BCS) classification prediction web-platform based on advanced machine learning algorithms with multiple molecular representations

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Background: The Biopharmaceutics Classification System (BCS) was proposed to evaluate the absorption rate and extent of oral immediate-release solid drug products by classifying drugs into four categories based on solubility and intestinal permeability. Such a concise classification system allows for biowaivers and reduces the need for clinical bioequivalence studies, thereby playing a crucial role in improving the efficiency of drug regulation and development. However, the accurate measurement of solubility and permeability is complex and costly, which limits the broad application of BCS. In the pre-formulation study, rapid determination of BCS classification is essential for drug candidate developability assessment and further formulation development decisions. In recent years, machine learning (ML) has demonstrated its value in establishing quantitative structure-property relationships (QSPR) by leveraging large amounts of data. The emergence of advanced ML algorithms and efficient molecular representations offer promising solutions for rapid in silico BCS classification through accurate property predictions.

Purpose: The present study aims to develop an open, user-friendly web platform based on high-precision compound property prediction ML models for pharmaceutical scientists to achieve batched and rapid BCS classification prediction of drug candidates.

Method: First, four molecular property datasets were integrated and cleaned, including logS, logP, logD, and logPapp, which are considered relevant to BCS classification. Next, to obtain the best model performance, six machine learning algorithms based on different principles were used for model training, corresponding to different dimensional molecular representations, including one-dimensional molecular fingerprints, descriptors, molecular graphs, and three-dimensional molecular spatial coordinates. Subsequently, the validated best-performing models were integrated for comprehensive BCS classification prediction and embedded into a web platform based on the MVC architecture.

Results: After screening 24 models for four property prediction tasks, the LightGBM model achieved the highest performance for solubility prediction, with an R^2 of 0.84. For permeability prediction, the AttentiveFP model outperformed others in predicting logP and logD with R^2 values of 0.96 and 0.76, respectively. The XGBoost model was the most accurate for the Caco-2 permeability task with an R^2 of 0.71, limited by the restricted data amount and high data complexity. When applied to additional validation sets of marketed drugs, the best-performing models achieved over 77% and 73% classification accuracies for solubility and permeability, respectively. On the comprehensive BCS classification task, our models also demonstrate superior performance compared to previous studies. Moreover, the well-trained models have been integrated into an efficient and user-friendly web platform. Users can rapidly obtain predicted BCS classifications with the prediction bias, as well as the basic calculated information and predicted properties for the queried molecules.

Conclusion: This study developed the first machine learning-based web platform for BCS classification prediction, assisting in high-throughput screening of drug candidates and early-stage developability assessment. This platform enables researchers to quickly determine the BCS classification of compounds, reducing the number of experiments required for decision-making. Furthermore, the use of this platform has the potential to significantly impact the entire drug design and discovery process by accelerating drug development, improving efficiency, lowering development costs, and advancing drug approval.

Aloe vera blended alginate-gelatin composite hydro film for diabetic wound healing application

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Diabetic foot ulceration is a life-threatening co-morbidity resulting from diabetes mellitus and possesses a tendency to progress into chronic wounds, in which leg amputation is imminent. The current study was designed to evaluate the additive effects of an aloe vera-alginate-gelatin (AV-ALG-GEL) composite film on diabetic wound healing. 0.3% w/v lyophilized aloe vera (AV) was blended with 3% alginate-gelatin solution along with 5% glycerol and cast as a film by drying at 37°C to be utilised for an in vivo study in a rat model. All the rats were diabetic induced using streptozotocin (45 mg/kg) and grouped into 2 groups: control and test. A 3.3 cm^2 excision wound was created on the dorso-lumbar region of the rats, whereby the control group was treated with alginate-gelatin films and the test group with aloe vera-alginate-gelatin films, respectively. The films for each group were changed every two days. After euthanasia with excess diethyl ether on the 16th day of post-wound creation, the wounded skin along with surrounding skin was harvested for hydroxyproline estimation and histopathology studies. The results indicated that the presence of aloe vera significantly increased the percentage wound closure rate significantly to control, evident from the increased hydroxyproline content in the wounded skin of the test group. The histopathological studies revealed that the distribution of fibroblasts was denser in the test group, resulting in greater deposition of collagen in the extracellular matrix than in the control. It is proven that the presence of aloe vera enhances overall diabetic wound healing; hence, AV-ALG-GEL film could be a promising candidate for diabetic wound healing.

Female-controlled non-hormonal contraceptive for on-demand prevention of pregnancies and sexually transmitted infections

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Background: Current marketed products provide limited choices for women to protect against unintended pregnancies and, simultaneously, prevent sexually transmitted infections (STIs). Moreover, socioeconomic factors further disadvantage women in low resource settings to access available products for such multipurpose prevention.

Purpose: The main objective of this research is to develop a non-hormonal, bioresponsive SMART hydrogel engineered with effective contraceptive and antimicrobial properties for female-controlled on-demand use.

Methods: A bioresponsive SMART hydrogel containing 0.5% (w/v) metronidazole (MTZ) was fabricated using conventional sol-to-gel transformation. Viscoelastic and mucoadhesive properties of the MTZ-loaded SMART hydrogel 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. Buffer capacity in the presence of SFS was measured using a DeltaTrak ISFET pH probe. MTZ-release from the drug-loaded SMART hydrogel was quantified in vitro using a validate HPLC method. Experiments were performed 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 properties significantly increased upon interaction of the drug-loaded SMART hydrogel with SFS, resulting in a 119% greater work of shear measured at a volumetric gel/fluid ratio of 1:1 (5.79±0.01 N×s vs. 2.64±0.01 N×s for gel only). The pH value of the gel phase measured under those conditions increased from pH 3.6 to 5.6. In comparison to the marketed vaginal Gynol™ II gel, mucoadhesive properties of the MTZ-loaded SMART hydrogel were 15-fold greater (4.47±0.04 N×mm vs. 0.30±0.06 N×mm, respectively). Kinetic drug release measurements revealed the presence of MTZ concentrations after 30 s that are in excess of the minimum inhibitory concentration reported for this antibacterial drug after vaginal administration in vivo.

Conclusion: Bioresponsive, MTZ-containing SMART hydrogel appears a promising novel, female-controlled choice for on-demand protection against unintended pregnancies and STIs. The results from these in vitro experiments support further assessment of this novel multipurpose prevention technology using validated in vivo models.

Encapsulation of lutein extracted from Gac in lipid based nanocarriers for eye health

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Background: Lutein is a carotenoid accumulating in the macula of the eye and it protects the macula by activation of antioxidant response. Gac (Momordica cochinchinensis (Lour.) Spreng) is a highly nutritious edible fruit and contains the high levels of lutein. Therefore Gac fruit peel can be used as a sustainable source of carotenoids. However, due to low aqueous solubility and chemical instability, lutein and other

carotenoids have low oral bioavailability following supplementation. Cubosomes have recently been proposed as potential drug carriers because they can (1) efficiently encapsulate poorly water-soluble drugs and enhance their solubility; (2) exhibit bio-adhesive properties with sustained release properties; (3) protect drug molecules and increase their duration of action.

Objectives: This study aimed to evaluate the efficacy of cubosomes in improving ocular bioavailability of lutein extracted from gac fruit peel.

Methods: Lutein cubosomes were prepared using monoolein and DOTAB. The characteristics of lutein cubosomes including hydrodynamic diameter, polydispersity index, and ζ-potential were measured using a Malvern Zetasizer Nano ZS. The entrapment efficiency, stability, releasing ability and bioaccessibility of lutein cubosomes on Retinal Pigmented Epithelial (RPE) cell and animal models were investigated using a validated HPLC method. Additionally, the cytotoxicity of lutein cubosome on RPE cells was assessed.

Results: The encapsulation efficiencies of lutein in MO-DOTAB was 75 ± 5% and the mean particle size was 136 nm. Stability studies indicated that lutein in cubosomes is significantly more stable at room temperature when compared to free lutein. Treatment of RPE cells with 2.5 to 50 µL/mL lutein cubosome did not show any significant cytotoxic effects. The uptake of lutein from cubosomes reach their highest amount after 24 h of incubation which was sustained for a further 48 h. In contrast, the cellular uptake of free lutein significant decreased after 24 h of incubation. Topical ophthalmic administration of lutein cubosomes resulted in a significant increase in lutein levels in the retina after 7 days of treatment.

Conclusions: The study highlights the use of cubosome technology to improve stability and bioavailability of lutein extracted from gac fruit peel. The findings can be applied to manage or prevent common oxidative stress induced eye diseases such as AMD and glaucoma.

In vivo anti-inflammatory activity in bleomycin-induced rats of quercetin loaded microspheres effect of alginate concentrations

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Acute respiratory distress syndrome (ARDS) is one of problems caused by infectious disease in the lung. The process of ARDS involves damage to the pulmonary capillary endothelium and alveolar epithelial cells due to the production of local pro-inflammatory mediators and causes a loss of integrity of the alveolar-capillary barrier. Although there is no specific therapy to stop the inflammatory process, one of the treatments for ARDS is to prevent lung lesions. Quercetin has an important role of anti-inflammatory for therapy in lung tissue due to infection with irritating substances.
The aim of this study is to formulate Quercetin microspheres using alginate polymers (1.5%, 2%, and 2.5%) called F1, F2 and F3 and ionic gelation technique. After formulating, in vivo anti-inflammatory activity was conducted.
In this research, Quercetin is expected to be an alternative treatment using microspheres delivery system. This study used bleomycin as an irritative inducer. In this study, 36 Wistar male rats were classified into 6 groups. Group 1 is a negative control group, group 2 was induced with bleomycin, group 3 was induced with bleomycin and Quercetin alone (drug free), 4th group was induced with bleomycin and microspheres F1, group 5 induced with bleomycin and F2 microspheres and the last group were induced with bleomycin and F3 microspheres. Histological examinations of the lungs and trachea in rats were conducted and inflammation results of each group were observed using histopathological scale forms both in the trachea and bronchial tubes and alveolar. In addition, cytokine levels (IL-6) from rat serum was measured using ELISA.
Microspheres showed that all formulas have a spherical shape and a smooth surface with diameter of microspheres of less than 5µm. Increasing the concentration of sodium alginate causes an increase in yield and entrapment efficiency, while for drug loading, there is no significant difference by increasing alginate concentrations. Recovered Dose value increased with increasing alginate concentrations but decreased the Emitted Dose and Fine Particle Fraction values. Mass Median Aerodynamic Diameter (MMAD) showed drug deposition in the tracheobronchial and secondary bronchial areas as much as 24%. The histopathological results of the trachea, bronchial, and alveolar rats found that free Quercetin and formula F1 produced the lowest inflammation results. However, the free quercetin group showed emphysema and experienced activation of the Bronchus Associated Lymphatic Tissue (BALT). Hence, the F1 showed the most optimal results. Quercetin microspheres had lower IL-6 levels than the bleomycin-induced group for one day of therapy suggested the antiinflammatory role in the Quercetin group.

In summary, differences in alginate concentrations affected the physical characteristics, aerosolization performance and in vivo efficacy of the microspheres. Further recommendation of the development of the inhaled formula by dry powder inhaler (DPI), excipients which contribute to the performance and stability is needed to prevent aggregation and increase the formula's efficacy when entering the lungs.

Study on preparation of phencynonate hydrochloride extended release tablets and its pharmacokinetics in beagle dogs

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The purpose of the research is to prepare phencynonate hydrochloride extended release tablets using double layer osmotic pump technology and to investigate its pharmacokinetics in beagle dogs. The single factor tests were adopt to optimize the formulations and preparation technology of drug layer, push layer, membrane in phencynonate hydrochloride extended release tablets. Orally single-dose double-period cross tests with administrated to beagle dogs were designed to investigate the bioavailability and bioequivalence of phencynonate hydrochloride extended release tablets. The drug release curves in vitro with optimized formulation of phencynonate hydrochloride extended release tablets fitted zero-order model. The equation of drug release was as follows: Q＝5.7787 t－5.7067, r＝0.9902. The relative bioavailability of phencynonate hydrochloride extended release tablets was 94.77 %, which was bioequivalent with phencynonate hydrochloride tablets in absorption degree. The Cmax is 3.9±0.678 μg·L-1, which was significantly lower compared with conventional tables (12.8±2.799 μg·L-1). The Tmax and MRT were 8.657±0.992 h and 12.653±1.964 h, respectively, which were significantly prolonged compared with conventional tables (1.25±0.284 h、6.426±0.726 h). Phencynonate hydrochloride extended release tablets based on osmotic pressure mechanism possessed obviously sustained release characteristics in vivo and in vitro. The optimized preparation has clear clinical guidelines and it shows broad prospect in development and application.

Physicochemical and microbiological stability of compounded clonidine hydrochloride oral liquid dosage forms in PCCA base, suspendIt

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Objective: To study the stability of extemporaneously compounded clonidine hydrochloride suspensions in the contemporary vehicle PCCA Base, SuspendIt. SuspendIt is a sugar-free, paraben-free, dye-free and gluten-free thixotropic suspending agent containing a natural sweetener obtained from the monk fruit. It thickens upon standing to minimize settling of any insoluble drug particles and becomes fluid upon shaking to allow convenient pouring during administration to the patient. The study design included two concentrations to provide stability documentation over a bracketed range for eventual use by compounding pharmacists.

Methods: A stability-indicating HPLC assay of clonidine hydrochloride in SuspendIt was developed and validated. Suspensions of clonidine hydrochloride were prepared in SuspendIt at 20-mcg/mL and 100-mcg/mL, selected to represent a range within which the drug is commonly dosed. Given the potent nature of the drug, a 2% triturate of clonidine hydrochloride in microcrystalline cellulose was used to prepare the samples. Samples were stored in plastic amber prescription bottles at two temperature conditions (5 deg C and 25 deg C). Samples were assayed initially, and at pre-determined time intervals as follows - 7, 14, 28, 42, 63, and 91 days. Physical data such as pH, viscosity, and appearance were also noted. Microbiological stability was tested. All measurements were obtained in triplicate.

Results: A stable extemporaneous product is defined as one that retains at least 90% of the initial drug concentration throughout the sampling period. Clonidine hydrochloride was stable for 91 days in SuspendIt at both temperatures. Drug concentrations were above 94 % of initial values. The pH measurements were consistent (5.06 to 5.09). Viscosity measurements ranged from 49.5 cPs to 52.7 cPs for most samples, and was sufficient to minimize any settling. The 100-mcg/mL sample had a slightly lower viscosity of 44.3 cPs at room temperature. This could be due to an interaction between the hydrochloride salt and SuspendIt. Given that clonidine hydrochloride is soluble in water, uniformity of drug concentration is independent of viscosity.

Conclusions: Compounded clonidine hydrochloride oral liquids at 20-mcg/mL and 100-mcg/mL concentrations in PCCA Base, SuspendIt were found to be physically, chemically, and microbiologically stable for 91 days at 5 deg C and 25 deg C. No commercial liquid dosage form of clonidine hydrochloride currently exists. The study therefore provides a viable compounded alternative for clonidine hydrochloride as an extemporaneous liquid dosage form, with an extended beyond-use-date.

Formulation studies of instant herbal tea (Claritea®)

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With increasing herbal tea consumption and fast-paced lifestyle, instant drink powders captured the interest of many due to its longer shelf-life and convenience in preparation by merely dissolving in water for less than five minutes. It could be prepared either through dehydration,

freeze drying, or spray-drying in which the latter is a well-established method for drying thermally-sensitive substances such as the anthocyanin abundant in Rubus rosifolius. Several studies revealed that anthocyanin is beneficial for boosting the immune system, controlling weight gain, relieving pain due to inflammation, and treating lifestyle diseases such as diabetes, hypertension, and cancer. In the Philippines, R. rosifolius was considered an agricultural pest because of its thorny characteristics and invaluable by local farmers until they were taught of its health benefits. This research study will greatly benefit the local farmers in Dolores, Quezon as it may create livelihood opportunities through partnership between Adamson University and Bangkong Kahoy Valley Nature Retreat and Field Study. Moreover, the initial findings may serve as basis for future researchers interested in isolating, purifying, and determining other health benefits of R. rosifolius.

An instant herbal tea (Claritea®) was formulated by incorporating a carrier agent to R. rosifolius fruit and leaf extracts before subjecting to spray-drying process. Its physicochemical properties, DPPH (2,2-diphenyl-1-picrylhydrazyl-hydrate) free radical scavenging activity, alpha-glucosidase inhibitory activity, stability, acute oral toxicity using experimental mice, and sensory evaluation & acceptability testing with 50 panelists were performed.

It was found that Claritea® has pinkish red color with sweet-tangy odor, sour with a slight sweetness in taste, pH 3.467, and moisture content of 4.58% which is lower because maltodextrin as a carrier agent is known to be hygroscopic that can easily absorb moisture. Moreover, spray-dried powders with moisture content lower than 7-8% have highly porous structure making it freely soluble in both hot & cold distilled water. Anthocyanins were efficiently extracted upon maceration with acidified water as its cell membranes were denatured upon contact to the solvent causing stabilization of anthocyanin-colored flavylium cation type. In addition, it has antioxidant properties with percentage inhibitions of 33.78% (31.25 ug/mL), 47.58% (62.50 ug/mL), 64.86% (125 ug/mL), 71.06% (250 ug/mL), and 72.02% (500 ug/mL). The antioxidant property of dissolved product is predicted to remain until 22 days based on the accelerated stability testing with set conditions of 40°C ± 2°C & 75 ± 5% relative humidity for three months. Its alpha-glucosidase inhibitory activity at 1000 ppm is 90.54% and safe to be consumed orally even at high dose of 45 g/kg with no remarkable lesions found in the liver, kidneys, and ovaries. Furthermore, Claritea® prepared as warm tea & chilled beverage is like slightly by participating panelists.

Hence, the formulated instant herbal tea (Claritea®) exhibited antioxidant and hypoglycemic properties, stable, safe to be consumed orally, and acceptable in terms of color, odor, texture, and taste.

Inhalable ebselen dry powder for respiratory tract infections

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Background: Respiratory tract infections (RTIs) are one of the major public health burdens and leading causes of death in the current world. Ebselen, a clinically safe organoselenium compound, has shown promising antimicrobial activity against many respiratory pathogens including SARS-CoV-2, Influenza A virus, Staphylococcus aureus,. Staphylococcus pneumonia, and Mycobacterium tuberculosis. The direct delivery of antimicrobials to the infection site is an efficient way to ensure better therapeutic activity with less adverse effects. This is achieved by using a lower, but more effective, drug concentration than other conventional dosage forms (oral/injectable). A dry powder inhaler (DPI) is one of the most promising approach for delivering drugs into the respiratory tract. DPIs are more stable, and can deliver a high dose of drugs for viral/bacterial infections than other widely used devices such as a meter dose inhaler (MDI) or nebulizer.

Purpose: The purpose of this study was to develop and characterize an inhalable dry powder containing ebselen.

Method: The inhalable dry powder containing ebselen was prepared by spray-drying technique and in the presence of different amino acids such as leucine, methionine, and tryptophan as amino acids can enhance the yield and aerosolization property of the dry powder. The ebselen (90% w/w) and amino acids (10% w/w) were dissolved in methanol to prepare the desired feed solution (0.8% w/v). The feed solution was then spray-dried using a Buchi B-290 mini spray dryer. The prepared powders were characterized by scanning electron microscopy, thermagoravimetric analysis, X-ray diffraction, fourier transform infrared spectroscopy to assess the morphology and particle size, water content, crystallinity, and drug-drug/drug-excipient interactions. The aerosol performance of the dry powder was assessed by a next-generation impactor (NGI) at a flowrate of 100 L/min when dispersed from an aerolizer.The cytotoxicity of the dry powders was determined on A549 cell line. The effectiveness was assessed against S. aureus and S. pneumonia using USA300 LAC and ATCC6305 cell line respectively.

Results: All the dry powders were crystalline and within the size range of 1–5 µm indicating their suitability for inhalation. Spray-dried ebselen (EBSSD) and themethionine and tryptophan-containing spray-dried ebselen (EMSD and ETSD) were all spherical whereas leucine-containing spray-dried ebselen (ELSD) showed wrinkle morphology determined by scanning electron microscopy. The emitted dose (ED) and fine particle fraction (FPF) were 72% and 48%

respectively for EBSSD. All the amino acids containing dry powders showed better aerosol performance than EBSSD. ELSD showed the highest ED of 84% and FPF of 68%. The spray-dried powders had similar cytotoxicity to the raw ebselen and the cell viability (IC50 value) values were between 100 – 200 µg/mL. Ebselen and the prepared dry powders showed similar potent antibacterial activity against S. aureus and S. pneumoniae with minimum inhibitory concentrations values of 0.31 µg/mL and 0.16 µg/mL respectively.

Conclusion: The inhalable dry powder containing ebselen was developed successfully and leucine containing ebselen dry powder showed the highest emitted dose and fine particle fraction.All the dry powders showed similar cytotoxicity and antibacterial effect to the ebselen raw material.

Studies on novel intranasal delivery system of second generation antipsychotic drug

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Aim and Objective: The objective of this investigation is to develop and evaluate specialized miniemulsions of Iloperidone using polysaccharide for improving mucoadhesion in intranasal delivery.

Method: Ultraviolet spectrophotometric method for Iloperidone, a second generation antipsychotic was developed in Methanol AR and Simulated Nasal fluid, pH 6.4 and validated for determination of drug content and during release and permeation studies. The development of miniemulsions involved screening of oils, surfactants and cosurfactants for their solubilizing capacity of Iloperidone. Iloperidone miniemulsions was optimized using Design of Experiments. Oleic acid, Tween 80, Transcutol and stearic acid were used to develop the Iloperidone miniemulsions. The optimized miniemulsions were subsequently coated with polysaccharides such as chitosan and derivatives, dextran etc and were further evaluated for particle size, zeta potential, surface morphology, in vitro mucoadhesion, in vitro release and ex vivo permeation.

Results and Discussion: The composition of optimized minemulsions was oleic acid and stearic acid as oil phase, Tween 80: Transcutol as Smix and water. Iloperidone miniemulsions were prepared by spontaneous emulsification method using ultrasonic processor. The optimized miniemulsions were translucent, stable, showed pH 5.5±0.5 and drug content 98.23±0.03%. Iloperidone miniemulsions could be surface coated with polysaccharide such as chitosan to improve mucoadhesive characteristics. Iloperidone miniemulsions showed negative zeta potential (-22.5mV±0.5) while coated Iloperidone miniemulsions presented positive zeta potential (+25.5mV±0.3) which confirmed surface coating of miniemulsion droplets with the polysaccharide. Iloperidone miniemulsions showed particle size 173 ± 0.3 nm while coated Iloperidone miniemulsions showed particle size 182.9±0.01 probably due to stabilizing effect exerted by stearic acid. In vitro studies showed that mucoadhesion of chitosan coated Iloperidone miniemulsions was 2.12-fold higher than Iloperidone miniemulsions. The in vitro release of Iloperidone using dialysis membrane (molecular weight cut off 14kD) in 250 ml, Simulated Nasal Fluid, pH 6.4, 32+2°C, 75 rpm from the miniemulsions and coated miniemulsions was 90.41 + 0.3 % and 72.02 + 0.21 % respectively at the end of 8 hours. The ex vivo permeation of Iloperidone using excised sheep nasal mucosa in 19 ml, Simulated Nasal Fluid, pH 6.4, 32+2°C, 50 rpm from the miniemulsions and coated miniemulsions was 708.43±0.043 µg/cm² and 945.05±0.023 µg/cm² respectively at the end of 8 hours.

Conclusion: The developed specialized Iloperidone miniemulsions showed improved mucoadhesion and in vitro studies indicated prolonged release. The ex vivo permeation studies showed improved permeation characteristics due to prolonged contact with sheep nasal mucosa. Thus, this can be a potential approach for direct nose to brain delivery due to improved mucoadhesion characteristics.

Residence time of loratadine prolonged after intranasal administration of its gel formulation

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Loratadine is a second-generation antihistamine administered orally to treat allergic rhinitis and urticaria. However, its oral administration can cause several side effects such as headache, dizziness, fatigue, and nausea. To address these issues, intranasal drug delivery is considered due to avoidance of the first-pass effect and improved bioavailability. In situ nasal gel formulation, in particular, is advantageous due to its sustained and controlled release of drugs.
In this study, an in situ gel formulation of loratadine was prepared and evaluated for its pharmacokinetic parameters through an in vivo experiment in rabbits and was compared with that of loratadine administered as intravenous and intranasal solutions.
The in situ gel exhibited the highest mean residence time when compared with intravenous and intranasal solution which indicates the accumulation of loratadine in a specific tissue for a longer period of time and exhibits its therapeutic efficacy. The pH of the formulation was within the

physiological range (pH = 6.60 ± 0.13). Drug plasma concentration significantly increased 6 to 8 hours after administration of gel ($p < 0.05$). The fraction of dose absorbed for the in situ nasal gel (F = 0.83) was 2.3-fold higher than that of the intranasal solution (F = 0.36).
Based on the results, the rise in drug plasma concentration from the in situ gel formulation appeared to be slower and more gradual compared to the intravenous and intranasal solutions. The incorporation of loratadine into in situ nasal gels may be beneficial for patients suffering from diseases affecting the nasal mucosa, such as allergic rhinitis, due to its improved bioavailability, convenient dosing, and easy administration.

Development and evaluation of microRNA-134 encapsulated cationic liposomes for chronic obstructive pulmonary disease.

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Background: MicroRNAs (miRNA) are non-coding ribonucleic acids that are involved in the regulation of gene expression and have been directly linked to several diseases including chronic obstructive pulmonary disease (COPD). Previous studies have shown that miRNA-based therapies can promote or inhibit miRNA expression and function. However, the clinical translation of naked miRNA delivery has so far proven challenging since these molecules have poor cellular uptake and are susceptible to nuclease degradation resulting in poor efficacy. To overcome these limitations, cationic liposomes (CLs) have been extensively explored as a delivery carrier system to protect and deliver miRNAs to the target cells. This work presents the initial data for the encapsulation of a potential biotherapeutic agent (miRNA-134 for mucus hypersecretion) in CLs for the application of COPD.

Purpose: To determine whether miRNA-134 can be encapsulated in CLs using the microfluidics method and to assess their physicochemical properties.

Method: CLs were fabricated at 8 mg/mL lipid concentration using the microfluidics method (NanoAssemblr® Benchtop, Precision NanoSystems Inc., Vancouver, Canada). The lipid components were dissolved in ethanol and miRNA-134 (5 nM) was dissolved in the aqueous buffer before injection. The two phases were simultaneously introduced into a Y-shaped staggered herringbone micromixer to produce CLs using a 5:1 aqueous:organic flow rate ratio and 5 mL/min total flow rate. CLs were then washed and concentrated using a centrifugal filter at 4000 g for 40 min at 4°C. CLs were measured for particle size, polydispersity index (PDI), and zeta potential using a dynamic light scattering (DLS) system (Malvern Zetasizer Pro, Malvern Panalytical, Worcestershire, UK); surface morphology was determined by cryogenic transmission electron microscopy (cyro-TEM) machine (JEOL JEM 2200FS Cryo-TEM, JEOL Ltd., Tokyo, Japan) and entrapment efficiency (EE) by RiboGreen assay.

Results: Using a simple and easy microfluidics method, we were able to encapsulate miRNA-134 in CLs. There was no statistical difference in physicochemical properties for miRNA-134-loaded CLs (MCLs) compared to the blank CLs (BCLs). MCLs had a suitable particle size (<150 nm) with a homogeneous particle distribution (PDI <0.3) and a cationic zeta potential. cryo-TEM showed that both MCLs and BCLs had spherical-like morphology with smooth surfaces and nanoscale particle size which were consistent with the results measured by DLS. The EE for the MCLs were found to be 9.6 ± 2.6 %.

Conclusion: This work demonstrates that MCLs can be fabricated using the microfluidics method with desired physicochemical properties for in vitro transfection studies. Future studies will be investigated incorporating CLs for their application in pulmonary delivery.

Analytical method development using LC/MS for SST01 oral formulation PK study

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Background: SST01 is a water-insoluble compound. A novel oral formulation was developed to improve its bioavailability. An analytical method using LC/MS with high sensitivity was required for the formulations' bioavailability evaluations.

Purpose: Development of an analytical method using LC/MS to evaluate the drug concentration in plasma.

Method: 100 µL of dog blank plasma sample was pipetted into a labeled Eppendorf vial. 10 µL internal standard (IS) solution and 10 µL of SST01 standard solution were added to each sample to give a final concentration in the extract of 3.13 ng/mL of IS. Votax each sample, then 210 µL of ice-cold methanol was then added to each vial, followed by vortexing and incubating in the freezer (-20 oC) for 30 minutes to allow full protein precipitation. The samples were then centrifuged at 5°C for 20 minutes at 16,000 rcf. The supernatant was then removed and placed into an LC-MS vial for analysis.

Results: The developed analytical method using LC/MS has good sensitivity. The method validation demonstrates acceptable accuracy and repeatability. The linearity was Y=-0.00102X2 + 1.80916X + 1.78687 (r=0.99791, r2=0.99582, weighting: 1/X2) (0.16-1562.5 ng/ml).

Conclusion: The developed analytical method is acceptable for the drug assay in the plasma.

Supersaturated solid self-nanoemulsifying drug delivery systems (Supersaturated S-SNEDDS) for the improved oral delivery of the poorly water-soluble and highly metabolised HIV antiretroviral, Lopinavir

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Background: Lopinavir is a HIV antiretroviral which inhibits the activity of a critical enzyme in the HIV lifecycle. It has exceptional virological activity, but poor solubility, poor permeability, and extensive first-pass metabolism by CYP3A4 enzymes present in the intestine and liver. Therefore, the need of developing optimised drug formulations to improve Lopinavir's solubility, permeability and bioavailability is required. This is where SNEDDS can overcome these limitations. SNEDDS are mixtures of oils, surfactants, and cosurfactants which spontaneously emulsify to form an oil-in-water nanoemulsion when exposed to GI fluids with a nanometric droplet size. They allow Lopinavir to be in a solubilised state when presented to the GIT, eliminating the limiting step of dissolution.

Purpose: This project will develop an optimised SNEDDS formulation using supersaturation, sonication and solidifying to enhance drug loading, reduce particle size, and improve stability, respectfully. The SNEDDS formulations will be physicochemical characterised and in vitro performance will measure drug release and solubilisation.

Method: Solubility in lipids, surfactants and cosurfactants were performed at various temperatures. Emulsification ability was performed using the inverted flask method. Supersaturation was performed by heating the preconcentrate at 60°C and loaded with Lopinavir up to 200%. Drug content was performed using the extraction method. Particle size, polydispersity index and zeta-potential were performed using Malvern Zetasizer. Identification of an oil-in-water emulsion was performed using various studies. Self-emulsification time forming a complete and uniform dispersed system was performed in 500mL distilled water at 37°C with a rotating paddle at 50rpm. Nanosizing was performed using a sonication bath. Solidification of liquid-SNEDDS were fabricated through physical mixing of a solid carrier and heated preconcentrate. The solid carriers were chosen based on highest absorption capacity and good flow properties. Surface morphology, structure, and size of solid-SNEDDS were determined though SEM. In vitro drug release and digestion were performed using a dissolution apparatus and a pH-stat apparatus.

Results: Lopinavir showed highest solubility in Capmul PG8 (lipid), Labrasol (surfactant), and Propylene glycol (cosurfactant), with the highest supersaturation obtained in Capmul PG8. Labrasol and Propylene glycol required the least inversions to produce a uniform emulsion obtaining the best emulsification ability. Particle size ranged from 142nm at 80% to 239nm at 200% drug loading. All SNEDDS displayed entrapment efficiencies of >69%, self-emulsified in <30 seconds, and were identified as oil-in-water stable emulsions. Parteck SLC and Aerosil R974 were chosen for solidification of liquid-SNEDDS. SEM images showed Parteck SLC as cubed-like smooth structures with diameters of 2-12µm and no visual changes with increased drug levels, and Aerosil R974 as spherical rough structures with diameters of 5-80µm and increased aggregation at higher drug levels. In vitro studies show both increase in drug release and solubilisation when formulated as liquid- and solid-SNEEDS.

Conclusion: The fabricated formulations show remarkably enhanced drug loading and solubilisation for Lopinavir. Supersaturated-SNEDDS is a promising formulation approach for drugs that require high doses due to low oral bioavailability. This potentially reduces the risks of long-term severe side effects that antiretrovirals cause and can improve the quality of life for people living with HIV.

A promising new oral delivery mode for insulin using lipid-filled enteric-coated capsules.

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The treatment of diabetes requires daily administration of the peptide insulin via subcutaneous (SC) injection due to poor stability following oral administration. Enteric capsules, designed to protect against low pH conditions in the stomach by providing a polymeric coating which only breaks down in the small intestine, have failed to significantly increase oral bioavailability for insulin. In parallel, amphiphilic lipid mesophases are versatile carrier materials which can protect encapsulated proteins and peptides from undesirable enzymatic degradation. Here we show the combined delivery capacity of a hydrated bicontinuous cubic lipid mesophase embedded within an enteric capsule. Animal studies demonstrated that the lipid filled enteric capsules could deliver insulin with bioavailabilities (relative to SC injection) as high as 99 % and 150 % for fast and slow acting insulin, respectively. These results provide a promising starting point towards further trials to develop an alternative, non-invasive mode for the delivery of insulin.

The impact of iron on fatty acid trafficking across the blood-brain barrier

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Alzheimer's disease (AD) is characterised by hallmark features such as amyloid-beta (Aβ) accumulation, neurofibrillary tangles formed by hyperphosphorylated tau, brain atrophy and sustained neuroinflammation. Apart from these hallmarks, a reduction in docosahexaenoic acid (DHA) has also been observed in the brain of people with AD. The de novo synthesis of DHA in the brain is limited. Hence plasma-derived DHA has to be transported across the blood-brain barrier (BBB) to maintain healthy brain DHA levels. There is plenty of evidence demonstrating the effects of iron on the pathology of AD but limited understanding of its impact at the BBB. The data from the present study are the first to demonstrate that increasing intracellular iron levels using ferric ammonium citrate (FAC) led to a 22% downregulation of fatty acid transporter protein (FATP1) at the protein level (via western blot) but not the mRNA level on human cerebral microvascular endothelial (hCMEC/D3) cells. Furthermore, upon performing functional studies, it was observed that FAC had no impact on the uptake of 3H-oleic acid (3H-OA) and 14C-DHA, but FAC significantly impacted on the efflux of 3H-OA and 14C- DHA from the hCMEC/D3 cells at various timepoints. While further studies are required to elucidate the molecular mechanisms underlying the FAC-induced downregulation of FATP1, these studies provide insight into the role of iron in regulating FATP1 at the BBB, which may have implications on the transport of fatty acids to and from the brain.

Improvement skin penetration capacity of drug by using microemulsion as a delivery carrier: formulation optimization and in vitro evaluation

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Linalool is aromatic oil with analgesic, antidepressant, anti-inflammatory, and anti-UVB-induced skin damages effect. The aim of this study was to develop linalool-loaded formulae for topical application. In order to quickly obtain an optimal drug-loaded formulation, the statistical tool of response surface methodology and a mixture experimental design with four independent variables were used to design a series model formulation, to analyze the effect of the composition on characteristics and penetration capacity of drug-loaded formulations, and to obtain an appropriate drug-loaded formulation. The results showed that the droplet size, viscosity and penetration capacity of linalool-loaded formulations were significant affected by the formulation components proportion. The skin deposition amount and flux of optimal linalool-loaded formulation expressively increased about 6.1-fold and 6.5-fold respectively. After 3 months storage, the physicochemical characteristics and drug level did not show significant change. The linalool formulation-treated skin showed non-significant irritation compared to the distilled-water-treated group. The results showed that microemulsions might be considered as potential drug delivery carriers for essential oil topical application.

Efficient tumour targeted drug delivery via unidirectional transendothelial pathway mediated by Golgi apparatus

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Background: Nanoparticles are widely used for tumour targeted delivery based on Enhanced Permeability and Retention (EPR) effect while the heterogeneity of EPR effect limits the delivery efficiency and thus therapeutic effect of nanoparticles. Recently, more attentions have been paid on EPR-independent transcytosis across endothelial cells in tumour vascular (transendothelial pathway) for improved delivery of nanodrugs to tumours. However, there are still problems for transendothelial delivery of nanoparticles including inefficient uptake by endothelial cells, apical recycling back to tumour vasculature and lysosomal degradation in endothelial cell.

Purpose: The study aimed to achieve EPR-independent unidirectional transendothelial delivery of intact nanoparticles to tumour via transcytosis mediated by Golgi apparatus and inhibition of apical recycling in endothelial cells.

Methods: Cell penetrating peptide (octaarginine, R8) and cystine ligand (Cys) co-modified nanoparticles (LRC) were constructed for improved transendothelial delivery of intact carriers to tumour mediated by Golgi apparatus. Berbamine (BAM), which is widely employed for recovery of leukocyte post chemotherapy in cancer treatment, was used in this study to inhibit apical recycling in endothelial cells.
The transcytosis efficiency and intracellular retention of nanoparticles was investigated on Transwell model of bEnd3 endothelial cells by measuring the nanoparticles transported to upper and lower chambers of Transwell along with those retained in cells.

To verify the involvement of Golgi apparatus in transcytosis and the influence of lysosomal degradation, the co-localization of nanoparticles with fluorescence labelled Golgi apparatus and lysosome was investigated via confocal imaging. The integrity of nanoparticle was studied via co-

localization of Nile red incorporated in nanoparticle membrane with CY5 labelled lipid (DSPE-PEG-CY5).

Results: Results on Transwell model revealed high cellular uptake of R8-modified liposomes (LR). However, most LR were retained in cells (75%) with less transcytosis. Confocal images showed high colocalization of LR with lysosomes, indicating lysosomal degradation in cells. Also, most of Nile Red was released from LR with less colocalizion with CY5-labelled carrier, revealing reduced integrity of LR post transcytosis.
In contrast, Cys modified nanoparticle (Lc) and LRC were mainly transported to upper chamber (70%) while BAM prompted the transport of LRC to lower chamber (75%). Inhibiting Golgi apparatus reduced the transcytosis of Lc and LRC to both upper and lower chambers. Also, confocal imaging revealed high localization of LC and LRC with Golgi apparatus. Therefore, it can be proposed that Cys enabled Golgi-mediated transcytosis of Lc and LRC. BAM could direct the transcytosis of LRC towards tumour. BAM had less influence on the tropism of LRC towards Golgi apparatus. Also, LC and LRC were intact post transcytosis proved from high colocalization of Nile Red with CY5-labelled carrier. Notably, Lc showed less cellular uptake than LRC which may be attributed to R8 ligand on LRC.

Conclusion: R8 and Cys co-modified nanoparticles (LRC) achieved efficient transendothelial delivery to tumour tissue with the help of berbamine (BAM). R8 prompted the cellular uptake of LRC. Cys enabled Golgi-mediated transcytosis of LRC across endothelial cell meanwhile prevented the lysosomal degradation. BAM improved the transcytosis of LRC to tumour tissue via preventing the apical recycling back to blood vessels.

Revolutionizing precision liver cancer treatment: Targeted and personalized chemotherapy delivery with biodegradable 3D printed bilayer films

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Background: Liver cancer cases and associated deaths are predicted to increase by about 55% by the year 2040[1]. Tumour resection is a common protocol, however, positive margins contributed to recurrence[2]. Although adjuvant chemotherapy improved survival rates, their systemic administration caused severe side effects. Targeted delivery of chemotherapy in the form of implants enhanced treatment outcomes while reducing toxicity. 3D printing (3DP) produces customized products, accommodating the heterogeneity of cancer where tailored dose, release and film geometry could be achieved.

Purpose: Development of biodegradable 3D printed bilayer films for the targeted delivery of combinational chemotherapy.

Method: Gels containing 5-fluorouracil (5FU) and cisplatin (Cis) were prepared separately, and used to print bilayer films using a bioprinter(Bio X, Cellink). The films were characterized and the effect of film design on the drugs' release was investigated. Additionally, the environmental impact of the printing process was evaluated and scored using the novel index of Greenness Assessment of Printed Pharmaceuticals (iGAPP) tool. Finally, HepG2 cell lines were used for cytotoxicity assessment.

Results: Characterization results revealed the absence of interactions among components of the film. The release profile of Cis was affected by film design, as less dense films released Cis faster (12 days) than denser designs (23 days). The release of 5FU was not affected by design changes, delivering its load in 24 hours. The printing process was modified to minimize environmental hazards and considered by iGAPP as an excellent green method. The bilayer films demonstrated significant cell death in HEPG2 cells and changes in the cell morphology indicating their potential for liver cancer treatment.

Conclusion: The printed films can directly deliver Cis and 5FU in the surgical cavity after tumour removal, reducing the risk of tumour re-growth. 3DP enables the precision therapy approach allowing for customization to meet individual requirements. Further in-vivo studies are required to optimize dosing.

Pharmacokinetic model for antibody-drug conjugates: An investigation of the properties of the linkers and the range of optimal cracking constants

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Background: High DAR (DAR > 6) ADCs typically exhibit strong anti-tumor activity in vitro, but often show poorer pharmacokinetic (PK) properties in vivo compared to lower DAR (DAR ≈ 4) ADCs. In addition, some ADC linkers have poor stability, leading to reduced DAR in circulation. Currently developed ADCs usually have two main types of linker systems: cleavable and non-cleavable. Trastuzumab deruxtecan (T-DXd, DS-8201a) is an anti-HER2 ADC, containing an anti-HER2 monoclonal Ab linked to an internal cysteine residue, and a cleavable peptide linker (4-(N-maleimidomethyl)cyclohexane-1-carboxylate) with 8 novel topoisomerase I inhibitor DXd molecules. The peptide linker is designed to be cleaved by lysosomal enzymes (such as cathepsins), which are highly expressed in tumor cells. Despite its high DAR, T-DXd has been reported to have good PK characteristics, high linker stability, and minimal distribution in normal tissues.

Objective: To build a PB-PK model of T-DXd with good PK characteristics, compare it with existing published PB-PK models of ADC drugs, and study the specific relationship between ADC drug linker stability data (cleavage constant, etc.) and its PD characterization through in vitro cell experiments and tumor-bearing mouse experiments, and further develop and explore the PK-PD model of the relationship between the ADC linker cleavage constant and its efficacy. By developing optimized models, determine the appropriate range of ADC cleavage constants in the medium, determine the optimal range of cleavage constants, that is, not easily collapsing in plasma and medium, strong permeability in tumor tissues, maintaining the complete ADC molecular form to reach the target, and easily binding to the target and being internalized and cleaved in tumor cells, and producing a better bystander effect, so that the design and development process of future ADC drugs can more accurately select suitable linkers.

Methods:

1. Model Establishment:
   Pharmacokinetic (PK) analysis: Use Phoenix WinNonlin for preliminary non-compartmental analysis of ADC plasma and tissue PK. PBPK model construction and fitting: Use Monolix for model parameter estimation and combined variance model two-compartment (ADC and dissociated active payload) model fitting, estimating the cleavage constant of the linker.
2. In vivo experimental validation:
   BALB/c nude mice and BALB/c normal mice intravenous injection of an appropriate amount of ADC drug, measuring normal mouse PK. HER2-positive human breast cancer cell line KPL-4 cells are cultured in RPMI medium and then sub cutaneously injected into BALB/c nude mice. Subsequently, at appropriate times, collect tumor, liver, lung, heart, kidney, bone marrow, and blood samples to measure different drug component concentrations and other evaluations, determining the PK of tumor-bearing mice, and providing comparative validation for the established model.
3. Topic Exploration:
   Change different ADC drugs to determine the most suitable linker cleavage constant and other parameters. By developing and optimizing models, the goal is to establish a better understanding of the ideal range of linker cleavage constants, allowing for more accurate selection of suitable linkers in the design and development process of future ADC drugs. This will help to ensure that ADCs maintain their integrity and efficacy while minimizing systemic exposure and adverse effects.

Framework nucleic acids loading siTNF-α for topical psoriasis treatment

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Background: Psoriasis, an autoimmune disease, plagues more than 1.25 million worldwide. TNF-α, as one of the major inflammatory cytokines, plays an important role in the pathogenetic process. TNF-α therapy has shown great success in better management of psoriasis. So far, TNF-α therapy mainly relied on antibody injection, which lacked compliance and convenience.

Purpose: Our work provided a novel topical TNF-α therapy by applying tetrahedral framework nucleic acid to deliver siTNF-α for psoriasis treatment.

Method: To pursue topical siRNA delivery, we chose framework nucleic acid (FNA) as the drug delivery system. siRNA with a sticky end will be integrated into FNA by complementary base pairing. To examine the ability of FNA to deliver siRNA, GAPDH as a model siRNA was applied. Both in-vitro and in-vivo tests were done to prove the concept. Lipopolysaccharide (LPS) induced Raw 264.7 cell line was used to prove the TNF-α knockdown efficiency of FNA-siTNF-α. Imiquimod (IMQ) induced psoriasis-like mice were applied to evaluate the treatment efficiency.

Results: siRNA with a sticky end was successfully integrated into FNA, which was characterized by 8% PAGE gel electrophoresis. On both the cellular level and mice model, FNA-siGAPDH showed higher GAPDH mRNA downregulation efficiency as well as transdermal efficiency than free siGAPDH. Further in the LPS-induced Raw 264.7 cell line, FNA-siTNF-α showed the advantage in lowering the mRNA level of siTNF-α compared to free siTNF-α. In the psoriasis-like mice model, after five-day FNA-siTNF-α cream topical administration, the symptoms of psoriasis were relieved from both desquamation and erythema aspects. The level of TNF-α, tested by qPCR and Elisa, was significantly reduced which indicated the successful delivery of siTNF-α.

Conclusion: This work provides a novel method for siTNF-α therapy by using framework nucleic acid as the drug delivery system. FNA-siTNF-α showed the potential in topical anti-TNF-α therapy for psoriasis treatment.

Does swallowing tablets with an extremely thick (IDDSI Level 4) medication lubricant alter drug absorption? A randomised, single-dose crossover study in healthy adults

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RFMO-04 - Rapid Fire Session Monday, P1-P2, September 25, 2023, 2:30 PM - 4:00 PM

Background: People who find it difficult to swallow whole tablets with water will commonly crush them and mix them with a food/fluid. Medication lubricants are a commercial pharmaceutical product designed to replace the food/fluid, providing a reproducible swallowing and dissolution environment for the medicine. These products are useful in aged care and hospital facilities where there can be a high proportion of patients requiring help to swallow medications. Results from in vitro-dissolution testing using medication lubricants and other thickening products indicates a highly significant reduction in dissolution rate of a of range drugs from crushed tablets, particularly noticeable with fluids classified as extremely thick (Level 4) using the International Dysphagia Diet Standardisation Initiative (IDDSI) framework.

Purpose: To determine whether swallowing whole or crushed tablets with an IDDSI Level 4 medication lubricant, Gloup Forte, causes the rate and extent of drug absorption to be significantly different to swallowing whole tablets with water.

Method: An open-label, randomised, single-dose crossover study in 19 healthy adults was performed, in which a standard oral dose of immediate-release paracetamol tablets prepared in six different ways was administered. Whole or crushed tablets were swallowed with water, or with the medication lubricant Gloup Forte vanilla or Gloup Forte lemon, both assessed as being IDDSI Level 4 thickness. Participants rinsed their mouth with water (and swallowed), and then brushed using an electric toothbrush for 4 minutes to remove residual paracetamol. Passive unstimulated saliva was collected at regular intervals from 5 minutes to 8 hours after swallowing and analysed using HPLC-UV. Pharmacokinetic parameters were estimated using a standard non-compartmental approach. A linear mixed-effects analysis of variance (ANOVA) model was used to perform statistical comparisons of Ln-transformed pharmacokinetic data (Cmax, AUClast) between treatment groups. The residual mean error was used to construct the 90% confidence intervals for the ratio of treatment means.

Results: For the whole tablets, co-administration with Gloup Forte was found to have no significant impact on paracetamol pharmacokinetics, with the 90% confidence intervals for AUClast and Cmax contained within the standard 80-125% limits. Administering crushed tablets with water or Gloup Forte had minimal impact on total paracetamol exposure (AUClast 90% CI: 89.7 – 113%, 79.7 - 99.9% and 88.0 - 110% for water, Gloup Forte/vanilla and Gloup Forte/lemon, respectively). However, crushing paracetamol tablets and caused a 35% increase in the maximal concentrations when administered with water (Cmax 90% CI: 109 – 170) and ~ 20-25% increase when administered with Gloup Forte (Cmax 90% CI: 95.3 - 147% and 102 - 157% for Gloup Forte/vanilla and Gloup Forte/lemon, respectively).

Conclusion: These IDDDSI Level 4 medication lubricants, Gloup Forte/vanilla and Gloup Forte/lemon, do not have a significant effect on paracetamol exposure when used by healthy adults to swallow whole or crushed paracetamol tablets. However, crushing tablets causes a significant increase in the rate of absorption, which is tempered by the use of Gloup Forte instead of water. These findings do not align with in vitro-dissolution test results, and we find no evidence that these products delay or reduce drug absorption.

Artificial intelligence in pharmaceutical sciences: Fad or future?

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Background: Artificial intelligence (AI) may be a game changer for pharmaceutical scientists. There is a growing interest in the uptake of modern AI technologies within different pharmaceutical systems. Many of these technologies utilise data to develop powerful predictive models that can be used to offer efficient solutions, minimise costs, and ultimately improve outcomes. However, there can be some concerning issues such as data availability, accessibility, and reproducibility.

Purpose: One approach that can offer a method of circumventing significantly trial-and-error experimentations and their associated costs and time during the experimental work in pharmaceutical research is to use modern AI technologies.

Method: Current work investigates the use of machine learning and mainly artificial neural networks (ANNs) in the

development of AI applications for the prediction of optimized pharmaceutical formulations.

Results: Preliminary results showed promising findings which can encourage the utilization of machine learning, particularly ANNs to design AI models for the prediction of optimised pharmaceutical formulations.

Conclusion: AI and machine learning have a hopeful future in pharmaceutical sciences. Future work aims to explore further the potentials of AI and machine learning technologies for wider pharmaceutical applications.

Optimizing a tissue-targeted nucleic acid therapeutic (DNA, mRNA, siRNA, CRISPR/Cas9) delivery platform with unique cell uptake properties for in vivo applications, and use in hard-to-transfect cells

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Gene delivery is a promising technique that offers a better way to prevent, treat and cure diseases that cannot be treated using traditional pharmaceutical approaches, and is an essential technique for improving our understanding of biological pathways and for drug development. Peptide-based gene delivery systems represent a safe and promising gene delivery approach, which can harness alternative means of cellular uptake compared to lipid nanoparticles, providing unique opportunities to improve their cellular uptake and cellular targeting capacity. However, these systems face challenges in terms of in vivo stability and targeted delivery to specific tissues. Our laboratory has developed multicomponent, peptide-based delivery systems for nucleic acid-based molecules (DNA, mRNA, siRNA, CRISPR), which feature a cationic peptide and/or polymer to condense oligonucleotides, an endosomal escape species to assist endosomal release, and a library of ligands for targeting receptors that are overexpressed on tumors to provide tumor-specific targeting. These systems can be readily assembled using an automated, high yielding Fmoc-peptide synthesis protocol. The combination of these systems with phospholipids generated formulations that efficiently packaged oligonucleotides into nanoparticles, were synergistic for cellular uptake, exhibited endosomal release, and demonstrated comparable transfection efficiency to the commercial reagent Lipofectamine 3000 in both serum and serum-free environments, while providing specificity for cell lines that overexpressed their targeted receptor. A variety of combinations of cationic, non-ionic and anionic phospholipid formulations have been assessed, to identify formulations that show maximum transfection efficiency in high serum containing conditions, as a model for in vivo applications. These systems have been further optimised by investigating the effects of varying the ratios of each component on particle size, cell uptake and gene expression, as well as incorporating various polymer-coatings to improve the stability and degradation tolerance of both the delivery system and genetic materials towards serum. Transfection experiments using plasmid DNA or mRNA encoding fluorescent proteins were performed on cancer cell lines, demonstrating that the gene delivery system was able to efficiently express the genetic material even in the presence of increasing serum concentrations, with specificity towards cell lines that overexpressed the targeted receptor. In addition, studies of individual systems, or mixtures, on hard-to-transfect cell lines, demonstrated their capacity to provide significantly improved uptake and expression in these cell lines when compared to Lipofectamine 3000. These findings suggest that these delivery systems could be used for in vivo, tissue targeted gene therapy applications in the future, and can provide scientists with a useful tool for transfecting hard-to-transfect cell lines for their research.

Saturated fatty acids modulate the expression of breast cancer resistance protein (BCRP) at the blood-brain barrier.

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Background: The ATP-binding cassette (ABC) transporter, breast cancer resistance protein (BCRP), is an efflux transporter at the blood brain barrier (BBB) that actively extrudes and limits the entry of a variety of xenobiotics into the brain. Typical dietary constituents of a high fat diet such as saturated fatty acids (SFAs) are presumably peroxisome proliferator-activated receptors alpha (PPARα) ligands and have been associated with a reduction in the bioavailability of BCRP substrates. As it has been suggested that PPARα ligands regulate the expression of BCRP, it was therefore hypothesised that a combination of SFAs would enhance the expression of BCRP at the BBB and reduce the delivery of CNS-targeted drugs.

Purpose: To assess whether a combination of SFAs [palmitic acid (PA) + stearic acid (SA) + myristic acid (MA)] can enhance the expression of BCRP at the BBB.

Method: Immortalised human cerebral microvascular endothelial (hCMEC/D3) cells were treated for 24 – 48 h with a range of equimolar concentrations of the SFAs based on the plasma free fatty acid concentration after a high SFA diet (i.e. 5-50 μM). hCMEC/D3 cell viability was assessed using an MTT assay. Western blotting was used to quantify the protein expression of BCRP in whole cell lysates (normalised to the signal of housekeeping protein, β-actin) as well as in membrane fractions, given that SFAs may also

affect localised changes to BCRP levels at the plasma membrane (normalised to the signal of housekeeping protein, Na+/K+-ATPase), affecting the efflux function of BCRP.

Results: Treatment of hCMEC/D3 cells with a non-toxic concentration of a combination of SFAs for 24- 48 h, however, only the treatment for 48 h treatment significantly ($P < 0.05$) enhanced BCRP protein expression 1.22-fold in whole-cell lysates. It is possible that this increase in total cell expression of BCRP was membrane-associated given that SFA treatment resulted in a 1.3-fold increase in BCRP protein expression in membrane fractions.

Conclusion: Our findings suggest that a combination of SFAs can enhance the expression of BCRP at the BBB. Based on our hypothesis, it is expected that this intervention may increase the function of BCRP at the BBB, therefore negatively impacting on CNS delivery of pharmacotherapeutics. In future studies, the function of BCRP at the BBB will be assessed by measuring the intracellular accumulation of the fluorescent BCRP substrate, Hoechst 33342. Due to the changes in BCRP protein expression, it is imperative to assess whether the observed changes induced by a combination of SFAs were due to modulation of ATP-binding cassette subfamily G member 2 (ABCG2), which is a gene encoding BCRP, transcriptional mechanisms and therefore ABCG2 mRNA would be quantified by RT-qPCR in the presence of SFA treatment.

An artificial intelligence decision system for solubilization strategies of small molecule drug candidates: lessons from approved drugs by partially supervised learning

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Background: As the low-hanging fruit gets picked competitively, the proportion of poorly water-soluble molecules in drug development pipelines continues to climb. Pharmaceutical scientists have developed various bio-enabling formulation strategies to improve the delivery efficiency of poorly water-soluble molecules. Such strategies based on different solubilizing principles suit compounds with different structures and properties. Choosing the appropriate formulation technique for a drug candidate in the early stages of formulation development is critical in improving drug development efficiency and reducing risk and costs. However, there currently needs to be more systematic studies to support solubilization strategy decisions for small molecules.

Purpose: Driven by the philosophy that "Structure determines nature and nature influences decisions", current research aims to establish correlations between a drug's structure and property with its appropriate delivery strategies through machine learning algorithms and to develop a user-friendly artificial intelligence (AI) system for formulation strategy decisions.

Method: First, the formulation techniques used in approved small molecule drugs were collated from the Orange Book, literature, and public reports. Oral drugs and injectable drugs were considered and handled separately. The highest single therapeutic dose information, the pKa data, and the RDKit descriptors were selected to represent drug molecules. Based on the information that approved drugs provide, the formulation strategy decision pathway can be briefly described as below: Decision 1 to determine whether a bio-enabling strategy is necessary; Decision 2a to decide if a drug can be developed in salt forms; Decision 2b to determine if each of the four commonly used bio-enabling strategies (solid dispersion, nanocrystals, lipid-based formulation, and cyclodextrin inclusions for oral drugs; organic solvents, surfactant micelles, liposomal formulations, and cyclodextrin inclusions for injectable drugs) is feasible for drugs need to be formulated as non-conventional formulations. It is worth noting that the above task lacks identified negative samples, which are typical of partially supervised learning tasks, more specifically, are positive-unlabeled (PU) learning tasks. For example, a poorly water-soluble drug that has yet to be approved as a solid dispersion formulation should not mean that it cannot be formulated as a solid dispersion. Given that, the PU bagging strategy was improved for scoring and relabeling such unlabeled data. After that, the interpretable random forest algorithm was selected from commonly used supervised learning algorithms for the total 12 classification tasks. Lastly, all well-trained models are systematically integrated into a user-friendly website for easy access.

Results: Twelve machine learning models were built with classification accuracy greater than 0.85 and the Matthews correlation coefficient (MCC) greater than 0.70. The model decision processes were visualized for rule extraction. The feature importance and feature differences across categories are analyzed and discussed. Moreover, a user-friendly AI system was built recommending formulation strategies for a given structure.

Conclusion: The current study developed the first artificial intelligence system for delivery strategy decisions of given structures, which enables efficient design-driven formulation development, opens up opportunities for improved new drugs, and demonstrates the potential and value of partially supervised learning in drug development.

Inorganic nanoparticles for overcoming biological barriers for advanced drug delivery

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Background/Purpose: Biological barriers, such as mucosal surfaces, epithelial junctions, and cellular membranes, can impede effective delivery of many drugs especially biologics.

Many biological activities occur at the nanoscale, and thus engineered nanomaterials are advantageous in modulating biological barriers to improve therapeutic outcomes. However, traditional polymeric and lipid nanoparticles suffer from low encapsulation efficiency, complex manufacturing and nonspecific drug release limiting their clinical utility.
My laboratory is internationally recognised in the development of programmable nanoparticles to tackle diverse drug delivery problems including overcoming biological barriers. Our patented porous silica-based platforms (MSNs) can be tuned at a nanoscale to create formulations with high loading capacity, targeted delivery of variety of drugs. [1, 2] Our group focuses on use of MSNs nanocomposites to overcome multiple biological barriers (Gut, Tumour, and BBB). We are particularly interested in effective oral delivery of hydrophobic drugs and macromolecules. For instance, by harnessing the high surface functionality of MSN we have prepared various pH and enzyme responsive drug delivery systems based on MSNs for targeting small intestine and inflamed gut. Additionally, we have evaluated the potential of library of silica particles in delivery of variety of small and macromolecules for the treatment of IBD, Diabetes, TB, and Brain Cancer. [1, 3-8]
Results: By tuning the nanoscale properties of silica nanoparticles we have shown that we are able to improve solubility and oral bioavailability of many small molecules (Budesonide, Curcumin, Resveratrol, Vorinostat) and antimicrobials (Vancomycin, Meropenem). By tuning the nanoscale surface roughness and pore-size we discovered that silica nanoparticles can act as a non-toxic permeation enhancer to improve oral delivery of biologics (Insulin, exenatide, IL-22) in vitro and in vivo. Very Recently, we have developed ultrasmall (30 nm) silica nanoparticles and shown its capability in the treatment of Glioblastoma[9].
Conclusion: We believe that inorganic nanoparticles such as MSNs and its hybrids have the potential to become all in one excipient/carrier for overcoming multiple biological barriers and has the potential to be translated into clinical practice in the future.

Enhanced hyperthermia therapy by magneto-photothermal dual-mode treatments in MWCNTs/Mn0.5Zn0.5Fe2O4 nanohybrids

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Alternative cancer treatments such as photothermal therapy (PTT) and magnetic hyperthermia (MHT) techniques have been studied to show promising potential as supplementary modalities. However, such techniques have their own limitations, for instance, high magnetic fluid concentration is required for the MHT, while the PTT has limitations in the treatment of deep-seated tumors due to low light penetration. Here, we report the development of MWCNTs/Mn0.5Zn0.5Fe2O4 (MZFC) hybrids for magneto-photothermal dual-mode cancer therapy. The obtained specific loss power (SLP) of the MZFC hybrids is found at least 1 order of magnitude higher, with improvement from ~ 19 W/g to 225 W/g, under the excitation of both an AMF of 6.4 kA/m and simultaneous NIR laser of 0.5 W/cm² irradiation. The synergistic exploitation of the photothermal and magnetic properties of MZFC effectively reduces the amplitude of the magnetic field and the NIR laser power density. Our in vitro cell experiments confirmed that the thermal effects mediated by the MZFC after endocytosis delivered enhanced cytotoxicity in the presence of dual excitation of NIR laser and AMF. These functional nanohybrids show promising potential for cancer therapy by using the PTT-MHT dual-mode magneto-photothermal techniques.

Machine learning Algorithms for predicting solubility of small-molecule compounds in organic solvents

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In the field of chemistry, the rapid selection of solvents is highly important, but accurate prediction of solubility remains a critical challenge. Therefore, the aim of this study was to develop machine learning models capable of precisely predicting the solubility of compounds in organic solvents. In this study, a dataset comprising over 5000 experimental temperature and solubility data of compounds in organic solvents was collected. To characterize the structural features, molecular fingerprints were utilized. The performance of lightGBM was compared against traditional machine learning techniques (PLS, Ridge regression, kNN, DT, ET, RF, SVM) as well as deep learning methods, for developing accurate models to predict the solubility of compounds in organic solvents at various temperatures. LightGBM demonstrated significantly improved overall generalization (logS±0.20) when compared to other models. The model also provided prediction accuracy (logS±0.59) for unseen solutes, which was similar to the expected noise level of experimental solubility data. Additionally, LightGBM revealed the physicochemical relationship between solubility and structural features, thereby contributing to a better understanding of the underlying mechanisms. The approach offers a means of quickly screening solvents and has the potential to be extended to predict solubility in different solvent systems.