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Abstracts

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PT1

THE ROLE OF THE LOW-TEMPERATURE PHASE TRANSITION IN HUMAN SKIN BARRIER LIPIDS ASSEMBLY AND PERMEABILITY

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Lipids in the *stratum corneum* (SC) form a vital barrier protecting the body from loss of water as well as from the environmental noxae. These barrier lipids undergo a known phase transition from a rigid orthorhombic (OR) to a looser hexagonal (HEX) arrangement at a temperature very close to the physiological.[1] The possible purpose of this lipid transition in skin physiology is unknown. The aim of this work was to test several hypotheses about this transition including its role in SC lipid assembly or barrier permeability properties.

Permeabilities of an isolated *ex vivo* human SC for water, a model permeant indomethacin, and a model macromolecule inulin were studied at 26 – 50°C. A decrease in activation energy above the OR-to-HEX transition was found for indomethacin but not for water and inulin indicating that the transition affected lateral solute movement along lipid layers. Monolayer studies with atomic force microscopy of *ex vivo* human SC lipids showed rearrangement into multilamellar islets protruding 10 nm above the lipid monolayer at temperatures close to the transition but not at room temperature. Thermal spectroscopy of the lipids pointed at crucial role of (de)hydration in the process of transition. Putatively, this transition acts as one of the homeostatic mechanisms in skin lipid barrier assembly.

The study was supported by the project "Grant Schemes at CU" (reg. no. CZ.02.2.69/0.0/0.0/19_073/0016935).

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PT2

COMPARISON OF THE LIQUISOLID TECHNIQUE AND CO-MILLING FOR LOADING OF A POORLY SOLUBLE DRUG IN INORGANIC POROUS EXCIPIENTS

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Recent approaches for improving the solubility of poorly aqueous soluble drugs focus on the utilization of mesoporous materials. [1] Drug loading into such materials can be achieved by different methods, and the success of any method depends on the carrier properties and/or the amount of API. [2] The aim of this study was to compare two drug loading methods of a poorly soluble drug using two inorganic porous carriers: magnesium aluminometasilicate Neusilin® US2 (NEU) and functionalized calcium carbonate (FCC). The objective was to obtain a substantial amount of drug load and evaluate the drug release from the carriers.

The loading of the model drug cyclosporine A (CyA) in the carriers was achieved by co-milling (Mixer Mill MM400, Retsch) or by preparation of liquisolid systems (LSS) using Transcutol® HP as a solvent. Drug-to-carrier ratios 15, 25, and 50 wt% were prepared, and subjected to drug release analysis in biorelevant media simulating fasted-state intestinal fluid (FaSSIF) at pH 6.5.

The results showed that loading CyA into mesoporous materials improved its release. Moreover, the LSS showed faster dissolution compared to the co-milled (CM) systems. A higher drug release of CyA from NEU formulations than from FCC formulations was also observed, presumably due to the larger surface area of NEU.

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PT3

PLGA NANOPARTICLES FOR THE LOCAL TREATMENT OF JOINT REPLACEMENT INFECTIONS

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Musculoskeletal infections which commonly accompany orthopaedic surgery are effectively treated with a combination of systemically and locally applied antibiotics in the form of targeted delivery systems with prolonged drug release. Antibiotics administered locally provide a high drug concentration at the target site. This approach benefits from minimizing systemic drug exposure and potentially reduces resistance development[1,2].

The aim of this work was to formulate and characterize vancomycin loaded PLGA nanoparticles (NPs) for impregnating bone grafts used in treatment of musculoskeletal infections. NPs were prepared by water-in-oil-in-water double emulsion solvent evaporation technique. Polyvinyl alcohol or poloxamer were used for emulsion stabilization.

NPs' size, polydispersity and zetapotential were determined using a Zetasizer Nano ZS. Encapsulation efficiency was estimated by UV-spectrophotometry directly by measuring the amount of encapsulated drug after dissolution of NPs in organic solvent and extraction of drug by water. Thermal behavior of blank PLGA nanoparticles and drug-loaded nanoparticles was studied using a DSC. The drug release into the PBS pH 7.4 at 37°C was measured.

As a result of our work, NPs up to 300 nm in size and polydispersity below 0.2 were successfully obtained. The created NPs will be used in further tests after optimalization of other parameters, such as encapsulation efficiency and drug loading.

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PT4

THE ANALYSIS OF LUBRICANTS‘ EFFECT ON THE WALL FRICTION ANGLE OF POWDER AND THE EJECTION FORCE OF TABLETS

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Lubricants are excipients added during tablet manufacturing to improve the flow of the bulk powder whilst additionally reducing the stickiness of tablets during compression. This presentation will focus on comparing the influence of different lubricants on the wall friction angle of powders and the ejection force (EF) of the resulting compressed tablets. The current standard lubricant in pharmaceutical manufacturing, Magnesium Stearate (MgSt), was compared with the performance of hydrophobic substances Stearic Acid (Sta) and Glycerol Dibenhate (GBD), the hydrophilic substances Sodium Lauryl Sulphate (SLS) and Sodium Stearyl Fumarate (SSF), and new lubricants, micronized Poloxamer 188 and 407 (P188 and P407).[1] The lubricants were blended with a model filler mixture using the raw substances, microcrystalline cellulose 102 and lactose monohydrate 1:1 (MCC102/L) via a sandwiching method for seven minutes using an ERWEKA 3D mixer to create 0.5, 1.0, 1.5 and 2.0 % (w/w) powder blends. Wall friction angle was measured using a Freeman FT4 Rheometer with samples of freshly mixed powder. EF was determined from 10 tablets that were compressed at 5, 7 and 10 kN and then ejected using a Zwick-Roell analytical tablet press. Results from the Freeman showed that the wall friction angle with most lubricants was decreased, with SLS and SSF showing similar results to MgSt. However, the addition of P188 or P407 only had little effect. The Zwick-roell showed all concentrations of SLS, SSF were effective at decreasing the EF compared with MgSt at all three compression forces. Additionally, P188 0.5% notably decreased EF at a 10 kN compression force.

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PT5

CORTICOSTEROID-LOADED PLGA NANOSPHERES FOR TREATMENT OF CHRONIC INFLAMMATION

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Corticosteroids are highly effective anti-inflammatory drugs with wide therapeutic use. Unfortunately, corticosteroid therapy is associated with severe side effects.[1] For safer and more effective anti-inflammatory therapy we tried to load corticosteroids into PLGA nanospheres (NSs) with predominant distribution into macrophages, key players in the development of inflammation.[2] Such formulations could be effectively employed in therapy of non-alcoholic steatohepatitis - chronic liver inflammation.[3] Using the nanoprecipitation method we prepared dexamethasone acetate-loaded PLGA NSs. The formulations were prepared in the size range 100-300 nm, which was proven as macrophage attractive, with maximum encapsulation efficiency about 20% determined by HPLC. Using the macrophage cell lines such as murine bone marrow macrophages and human macrophages (differentiated THP-1 cells) we observed effective reduction of the pro-inflammatory cytokines levels e.g. TNF-α and IL-1β by our NSs. Experiments were performed on lipopolysaccharide-induced inflammation model and no signs of cytotoxicity were observed. Furthermore, we tested our NSs labelled with fluorescent dye on *in vivo* models for accumulation studies. We observed fluorescence intensity of prepared NSs by IVIS Imaging System and the spectral cell analyzer. We were able to verify specific delivery of prepared NSs into liver and preferential accumulation in proinflammatory macrophages.

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PT6

GLYCEROL AND ITS INTERACTION WITH SKIN LIPIDS IN *IN VITRO* MODELS

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Glycerol is one of the natural moisturizing factors (NMFs) present exclusively in the stratum corneum (SC).[1] By holding water, even when the skin's outermost layers are exposed to low humidity, NMFs biologically enable the maintenance of skin hydration and produce plasticized SC that resists mechanical stresses.[2] This study investigates the role of glycerol on the microstructure and permeability of isolated-skin lipids in *in vitro* models. Preliminary results showed that lipid models containing glycerol could retain more than 75 % of the initial water loaded during the annealing over a 3 h period at room relative humidity (RH). Permeation studies indicated reduced indomethacin permeability compared to the control, without affecting water loss. Moreover, quartz crystal microbalance with dissipation monitoring (QCM-D) revealed comparable sorption isotherms between control and glycerol-containing models but more rigid and thinner films were created in the presence of the NMF. Such rigidity was confirmed by atomic force microscopy (AFM) studies at 25 % and 90 % RH.

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PT7

COMPARISON OF MELOXICAM COPROCESSED MIXTURES SPRAY DRIED FROM WATER OR ETHANOL

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In this study, two spray dried mixtures containing the same poorly water-soluble model drug meloxicam (MLX) were prepared. The effect of used solvent (water or ethanol) on the dissolution rate of MLX was investigated. The constant ratio of MLX, sodium lauryl sulfate (SLS), and chitosan (CHIT) 1 : 150 : 250, respectively, was used. In the aqueous system, MLX dissolution was improved by micellar solubilization using surfactant SLS; then the excipient CHIT was suspended in the mixture (SDML). SDML was spray dried by Niro atomizer D-400 Mobile Unit Minor. The ethanolic system (ethanol 96 % v/v) was prepared by dissolving MLX in ethanol, consequently SLS was added, and CHIT was suspended in the mixture (SDMO). SDMO was dried by Mini Büchi spray drier B-290 with Inert loop B-295.

Obtained products were characterized primarily by a flow through cell (USP 4) to estimate the dissolution rate of MLX. The particle size, size distribution (laser diffraction), and the shape (scanning electron microscope, SEM) of co-processed products were characterized; the crystallinity of a drug was studied by differential scanning calorimetry (DSC), modulated differential scanning calorimetry (MDSC), X-Ray diffraction (XRD), and Fourier transform infrared spectroscopy (FTIR). As the results showed, the amount of dissolved MLX increased by more than 80 % within 5 minutes compared to the raw MLX, while no substantial difference between mixtures was found. Deagglomerated MLX particles spread onto the surface of CHIT are better available for liquid medium and thus the highest dissolution rate is noticed in the first 60 seconds. No change of MLX crystalline form was observed, probably because of the excess of SLS and CHIT that covers the signal of MLX. In conclusion, spray drying of the aqueous and ethanolic solution of MLX solubilized by the SLS in a presence of CHIT carrier showed a pronounced effect on the dissolution rate of MLX.

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PT8

TOWARDS THE RATIONAL DESIGN OF INTRANASAL MUCOADHESIVE FORMULATIONS.

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Hyaluronic acid (HA) is a mucopolysaccharide known to interact with various mucosal surfaces therefore prolonging the resident time of formulations and ensuring the sustained release of therapeutics[1]. Despite its mucoadhesive nature, little is known about the mechanism of interaction with the mucosal surface. In this work, mucin from porcine stomach was employedas a model to study the interaction with hyaluronic acid, or its derivatives using rheology and isothermal titration calorimetry (ITC). With ITC, we demonstrated the dominance of hydrogen bonding[1] as the primary mechanism underlying its interactions with mucin coupled with conformational changes in both macromolecules. HA and the two derivatives (tyramine and 5-hydroxytryptophan) of HA followed similar mechanism. Upon mixing of HA or its derivativeswith mucin, the so-called rheological synergism[2] was established a phenomenon depicting the entanglement of polymeric chains. Native hyaluronan possessed the highest magnitude of interaction followed by tyramine and 5-hydroxytryptophan derivatives.

The study was supported by the European Union's Horizon 2020 research and innovation program under the Marie Skłodowská-Curie grant agreement No. 956977

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PT9

FORMULATION AND EVALUATION OF ORODISPERSIBLE TABLETS CONTAINING CAPTOPRIL, TRAMADOL, AND DOMPERIDONE IN COMBINATION WITH CO-PROCESSED EXCIPIENTS

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This work focused on preparing orodispersible tablets (ODTs) containing mannitol-based co-processed dry binders Prosolv® ODT G2, Ludiflash®, and Parteck® ODT in combination with active pharmaceutical ingredients tramadol, captopril, and domperidone by direct compression.

Prosolv® ODT G2 showed high energy of plastic deformation due to the content of microcrystalline cellulose. Parteck® ODT provided compact tablets due to the content of granulated mannitol. Tablets containing Prosolv® ODT G2 with captopril or domperidone and Parteck® ODT with domperidone met the requirements for ODTs production, i.e., friability ≤ 1% and disintegration time ≤ 180 s, fast wetting time, high water absorption ratio, and adequate tensile strength. Tramadol formulations did not meet sufficiently short disintegration time due to low porosity, which was observed by microtomography and scanning electron microscopy. The results of disintegration time point to the significant difference between the pharmacopeial method and BJKSN-13[1] method, with the disintegration time being longer when tested with the BJKSN-13 instrument.

The study was supported by the Funding Agency of Charles University under Grant SVV 260 547.

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PT10

DEVELOPMENT OF PLGA NANOPARTICLES FOR TARGETED DELIVERY OF OBETICHOLIC ACID

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Nanoparticles can effectively encapsulate a wide range of therapeutic and diagnostic agents to deliver them into specific cells, reducing their non-specific action and enhancing biological activity. PLGA is a biodegradable aliphatic polyester-based tunable polymer, approved by FDA and EMA as an excipient for parenteral administrations [1]. The aim of the work was to develop PLGA nanoparticles with incorporated FXR agonist (obeticholic acid), for the targeted delivery to macrophages for the treatment of metabolic liver disorders. Desired nanoparticles were in the size range between 100 nm to 300 nm. Nanoparticles were prepared by a nanoprecipitation method and size, polydispersity, and zeta-potential were determined. Spectrophotometrical and HPLC assay for OCA was developed. OCA was extracted from PLGA nanoparticles using an ethanol/acetone extraction system. The relationship between the size and the polydispersity index of prepared PLGA nanoparticles and different pH of water phase, used during nanoprecipitation has been studied. As a water phase, buffers with various pH ranges were used. For PLGA 50:50, with the increasing pH from 2.5 to 10, size decreases from 189 ± 3.87 nm to 42 ± 1.51 nm. For PLGA 75:25 with the increasing pH from 2.5 to 10, size decreases from 194 ± 2.27nm to 35 ± 0.74 nm. In vitro release of OCA from PLGA nanoparticles was studied. At physiological pH (7.3), around 86.63 % ± 0.61 % OCA was released from OCA-loaded PLGA nanoparticles in a 4 h study. At lysosomal pH (4.5) around 88.27 % ± 1.67 % OCA was released from OCA-loaded PLGA nanoparticles in a 355 h study.

The study was supported by GA UK grant No. 1348120 and SVV 260 547.

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PT11

INTRODUCTION OF AN INTRINSIC SURFACE AFFINITY RANKING OF DRUGS ON SILICA SURFACES

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In the last two decades, there has been an increasing interest among pharmaceutical scientists in using mesoporous silica-based drug delivery systems [1]. The increased attention is directly connected to the carrier's unique ability to stabilize non-crystalline drugs confined within mesopores. In addition, these formulations trigger supersaturation upon drug release and thereby enhance the oral bioavailability of poorly water-soluble drugs. However, there is a need to better understand drug-silica interactions to further harness this type of formulation technology. While in the presence of water, hydrophobic effects can cause molecular drug adsorption of drugs; an intrinsic surface affinity is given by the free energy of molecular ad-/desorption. The present mechanistic study successfully compared the results of the inverse gas chromatography (IGC) using volatile solvents and a non-ordered mesoporous silica grade with results from molecular modeling. A presented model includes enthalpic interactions from molecular mechanics and an entropic part from an empirical relationship with molecular descriptors (τ and HBN, see Myrdal et al. [2]). The introduced concept should serve the ultimate goal of bringing mechanistic insights as well as practical guidance to formulators as it provides an intrinsic affinity ranking to mesoporous silica.

This study was supported by the Charles University Grant Agency (Grant No. 337622/2022).

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DEVELOPMENT OF PLGA BASED FILM FORMING SYSTEMS FOR TOPICAL CBD DELIVERY

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This work focuses on formulation of film forming systems (FFSs) based on PLGA derivates with decreased hydrophobicity for topical delivery of cannabidiol (CBD), a naturally occurring substance with promising results in therapy of various inflammatory and auto-immune skin dissorders.[1] Besides plasticizers ethyl pyruvate, methyl salicylate or triacetin whose compatibility with PLGA was already examined,[2] a novel substance, bacterial-derived extremolyte ectoine will be tested for plasticization effect. It has a strong ability to bind water molecules and thus form a protective layer around proteins and biological membranes. This effect is successfully used in treatment of inflammatory diseases affecting skin or mucosa.[3] Various solvents were screened to identify biocompatible, non-toxic, sufficiently volatile candidates compatible with the film components and suitable for their dissolution. Based on the obtained results, acetone and ethyl acetate were selected for further development. The rheological and adhesive properties of prepared FFSs will be tested using previously developed methods. In situ formed films will be characterized with DSC, FTIR and SEM imaging.[4] Finally, the dissolution of CBD and PAMPA testing will be performed.

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PT13

OLIGONUCLEOTIDE LOADED HYBRID NANOPARTICLES FOR CHRONIC LIVER INFLAMMATION MANAGEMENT

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Naked siRNA cannot be administered to an organism by itself due to non-specific distribution, fast degradation by endonucleases and poor cell-uptake.[1] This project's aim is the preparation and biological evaluation of a fully biodegradable, biocompatible and macrophage specific nano-drug delivery system for anti-inflammatory siRNA as a potential platform for chronic inflammation therapy. The first step in creating a suitable delivery system was to prepare a complex composed of oligonucleotides and cationic lipid, namely 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) by Blight-Dyer technique to give the naturally hydrophilic oligonucleotide molecule overall hydrophobic properties. Consequently, oligonucleotide-loaded nanoparticles based on poly(lactic-co-glycolic) acid were prepared by simple and rapid nanoprecipitation method. Resulting oligonucleotide loaded hybrid nanoparticle formulation properties is 89,68 ± 2,62 % encapsulation efficiency and the particle size of 191,9 ± 10,24 nm. Currently the focus is on evaluation of physico-chemical properties as well as drug release profile and cytotoxicity of the formulation. Drug release experiments have shown the prolonged release of oligonucleotide with initial burst resulting in plateau in around 144 hours. *In vitro* experiment on differentiated THP-1 cells has proven that this nanoparticulate formulation is not toxic for human cells.

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