FACULTY OF PHARMACY
IN HRADEC KRÁLOVÉ
Charles University

12th Postgraduate and Postdoc Conference

1. - 2. February 2022

Abstracts

Section 7 - Pharmaceutical Technology

EFSA-CDN

This conference is supported by the EFSA-CDN project (Reg. No. CZ.02.1.01/0.0/0.0/16_019/0000841)
co-funded by the European Union

EUROPEAN UNION
European Structural and Investment Funds
Operational Programme Research,
Development and Education

MINISTRY OF EDUCATION,
YOUTH AND SPORTS

PT1

CORTICOSTEROID-LOADED PLGA NANOSPHERES FOR MACROPHAGES TARGETING: A TOOL FOR INFLAMMATION MANAGENT

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Macrophages play an important role in maintaining homeostasis of the organism and they influence the progression of various diseases, including chronic inflammation or immune system disorders[1]. Therefore, macrophages-specific drug delivery system seems to be interesting therapeutic tool for wide variety of diseases[2]. In our project we investigate PLGA nanospheres (NSs) as potent macrophage-specific drug delivery system. We have prepared several different corticosteroid-loaded PLGA NSs using both nanoprecipitation and emulsification solvent evaporation methods. The encapsulation efficiency of prepared NSs was determined by HPLC. Prepared formulations were tested in primary murine bone marrow-derived macrophages and human monocyte cell line THP-1. The cytotoxicity was evaluated using the MTS assay. The inflammatory response of the cells was determined by RT-qPCR assay of proinflammatory and anti-inflammatory cytokines. Prepared nanospheres reached a maximum encapsulation efficiency of corticosteroids 20% and showed the ability to effectively suppress of production of pro-inflammatory cytokines in lipopolysaccharide-stimulated proinflammatory macrophages. No effects of nanospheres on cellular viability was observed.

The study was supported by SVV 260 401, GAUK 1586119, GAČR 19-14497S

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PT2

IMPROVING OF MELOXICAM DISSOLUTION RATE USING SPRAY DRYING PROCESS

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In this work, spray drying method was used to improve the dissolution rate of a poorly soluble model drug meloxicam (MX). MX was dissolved in purified water by micellar solubilization using surfactant sodium lauryl sulphate (SLS). Consequently, drug carrier chitosan (CHIT) was suspended in the mixture and the prepared suspension was spray dried at temperatures 170 °C, 190 °C and 210 °C using a 1.4 mm-diameter nozzle. Obtained particles were evaluated by scanning electron microscope (SEM) for shape, by differential scanning calorimetry (DSC) for thermal characteristics, and by dissolution studies for drug release (USP 4 flow through cell method). The results showed an increase in the drug dissolution rate by more than 60 % within 5 minutes compared to the pure MX for spray dried mixtures while the increase in dissolution rate by 30 % compared to the pure MX was noted for the physical mixture. Maximum dissolution rate in first 60 seconds is caused by the improved contact of medium with deagglomeration of MX particles due to the adhesion onto the surface of chitosan particles and their better availability. No change in MX crystalline form was observed by thermograms. However, the surfactant effect should be considered as well. In conclusion, the spray drying of the micellar aqueous solution of MX solubilized by the addition of SLS in a presence of CHIT particles showed a pronounced effect on the dissolution rate of MX.

The study was supported by the Funding Agency of Charles University under Grant SVV 260547.

PT3

SYNTHESIS AND STUDY OF AMPHIPHILIC DERIVATIVES OF HYALURONIC ACID

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Hyaluronic acid (HA) is a natural polysaccharide consisting of *D*-glucuronic acid and *N*-acetyl-*D*-glucosamine units linked by glycosidic bonds. In the human skin, HA is present in the *dermis* and *epidermis*, with the *dermis* containing a more significant proportion. During senescence, the reduction in HA production further impacts the skin's hydration and flexibility.[1] Therefore, topically applied HA could help reduce these issues.

HA does not easily cross the *stratum corneum* (SC) as a polyanion because of the hydrophobic barrier lipids. One commonly used approach to applying HA into the skin is to prepare HA derivatives with covalently bonded lipophilic moiety. Therefore, a novel amphiphilic HA derivative has been synthesized in this work. The prepared amphiphilic derivative can form polymeric micelles, which can transcellularly cross the SC with encapsulated lipophilic substance.[2] Furthermore, the dependence of critical aggregation concentrations, pyrene binding constants, particle size, curcumin encapsulation efficiency on the degree of substitution and molecular weight have been investigated. Moreover, penetration experiments of amphiphilic HA derivatives with an encapsulated fluorescent probe (Nile red) were performed *in vitro* in Franz cells using porcine ear skin. Penetration experiments were evaluated using confocal microscopy.

The study was supported by GAUK 332821 and SVV 260547.

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PT4

IMIQUIMOD IN LIPOSOME-DENDRIMER SYSTEMS: SOLUBILITY AND SKIN PERMEABILITY

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Imiquimod (IMQ) is a topically applied imidazoquinoline prescribed for the treatment of several skin diseases, like actinic keratosis and basal cell carcinoma. Traditional formulations deliver a significantly low IMQ amount (~2%) due to poor solubility (<0.002 mg/ml) and low cutaneous permeability.[1] Different studies have demonstrated the efficacy of dendrimers on the improvement of the solubility of poorly soluble drugs. [2] This work aimed to investigate the effect of a new type of dendrimers on the solubility and skin permeability of IMQ. Different concentrations and generations (G0, G1, G2, and G3) of dendrimers were tested for their effect on IMQ's solubility. The impact of dendrimers was evidenced as their use resulted in a 4×10^{3}-fold increase in the drug's solubility. The optimal preparations were combined with liposomes and the skin permeation profile of the formulations (with or without liposomes) was examined. G0 with a S_{IMQ}~7.5 mg/ml provided a 10x higher amount of IMQ to the human epidermis *ex vivo* than the commercial product (6x higher IMQ concentration). The liposomes' addition resulted in a lower IMQ amount in the epidermis probably due to the lower concentration in the purified liposomes. In conclusion, the findings of this study indicate that dendrimer containing systems may be a promising alternative for IMQ's topical administration.

The study was supported by the Czech Science Foundation (GACŘ 19-09600S) and Charles University (GAUK 274221 and SVV 260 547).

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PT6

BIODEGRADABLE SIRNA LOADED NANOPARTICLES FOR CHRONIC INFLAMMATORY DISEASES THERAPY

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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 initial focus at this stage is on preparation of nanoparticles and optimization of granulometric properties and drug loading efficiency. Naked siRNA cannot be administered to an organism by itself due to non-specific distribution, fast degradation by endonucleases and poor cell-uptake.[1] The first step in creating a suitable delivery system was to prepare a complex composed of oligonucleotides and cationic lipids, namely dimethyldioctadecylammonium bromide (DDAB) or 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) by Blight-Dyer technique to give the naturally hydrophilic oligonucleotide molecule overall hydrophobic properties. Consequently, nanoparticles based on poly(lactic-co-glycolic) acid (PLGA) were prepared by nanoprecipitation method. During nanoprecipitation, various conditions were examined. The solubility of the complex in different organic solvents was investigated along with various surfactants in a water phase for stabilization of created nanoparticles. The most suitable solvent mixture for the complex was chloroform and acetone 1:19. Pluronic F-127 in concentration 0,5% was chosen as a surfactant based on preliminary results and under these conditions the resulting encapsulation efficiency for the model oligonucleotide was 89,68 ± 2,62 % and the size of the particles was 191,9 ± 10,24 nm.

The study was supported by SVV 260 401 and Czech Scientific Foundation project no. GA19-14497S

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PT7

DEVELOPMENT OF NANOFORMULATIONS FOR TARGETED DELIVERY OF BILE ACID DERIVATIVES

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Farnesoid X receptor (FXR) is a nuclear receptor expressed mainly in hepatic and intestine cells. It's a key regulator of numerous metabolic pathways, including inflammation and fibrosis[1]. Bile acids and their derivatives, for example obeticholic acid, are natural agonists of FXR[2]. When binding to FXR, they can suppress the inflammation and fibrosis in the liver. In the case of systemic administration, obeticholic acid has numerous side effects. To reduce side effects and to enhance site specific action, development of liver-targeted delivery system for obeticholic acid (OCA) is could be a potent tool for liver inflammation management. Nanoparticles were prepared using nanoprecipitation method and size, polydispersity and zeta-potential was determined. In this study, relationship between the size and polydispersity index of PLGA nanoparticles with different water phase parameters (pH, type of buffer and ionic strength) was also studied. Moreover, spectrophotometrical assay for OCA was developed and validated. HPLC assay for OCA was also developed. In order to estimate the encapsulation efficiency of OCA in PLGA nanoparticles, ethanolic extraction method for OCA was developed and optimized. We discovered that with the decrease of pH from 7 to 3 leads to nanoparticles size increase from 80 nm till 175 nm respectively. Extraction efficiency was averaging 93%. An average encapsulation efficiency of OCA in PLGA nanoparticles was 73%.

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

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PT8

SHEAR AND AVALANCHE TESTING: EVALUATION OF MELOXICAM BINARY MIXTURES FLOWABILITY

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Flow behaviour of pharmaceutical powders is predominantly governed by interparticle cohesion.[1] The aim of this work was to study the cohesion of six binary powder mixtures containing 5% - 50 % of a model drug meloxicam (MX) and the excipient alginic acid (AA) and to elucidate a possible relationship with dynamic flow properties. MX particles were characterized by medium particle size x_{50} = 3.7 μm and large specific surface area S_{BET} = 2.09 m^2/g; contrary, AA particles were larger x_{50} = 57.9 μm with the lower S_{BET} = 0.39 m^2/g. Powder mixtures were prepared by physical mixing (3D shaker mixer) or co-milling (an oscillatory ball mill). The energy to break an avalanche[2] BE (Revolution Powder Analyzer) was correlated with the cohesion (an annular ring tester ShearScan). Cataracting avalanche regime showing poor flow properties related well with higher cohesion (1.87 kPa) and energy to break an avalanche (59.9 mJ/kg) of MX, while AA having the lower cohesion (0.31 kPa) and break energy (45.0 mJ/kg) showed acceptable flow with cascading behaviour. The cohesion and BE of MX binary mixtures increased with the higher content of the drug; the linear relation was detected with the coefficient of determination R^2 = 0.731. The cohesion was not influenced by the method of mixture preparation.

The study was supported by the Charles University Grant Agency (Grant No. 268120/2020; Grant No. SVV 260 547), by Zentiva, k.s. and by The Parc.

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PT9

STUDY OF THE EFFECT OF WATER ACTIVITY ON THE KINETICS OF THEOPHYLLINE MONOHYDRATE DEHYDRATION USING A MULTIVARIATE STATISTICAL APPROACH

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During formulation development, manufacturing and storage, pharmaceuticals are exposed to variable conditions. It has been shown that one-third of organic solid substances show crystalline polymorphism under normal pressure and further one-third of API can form hydrates[3]. Since the API can undergo phase transformation from anhydrate to hydrate depending on the surrounding environment[2] it can dramatically affect the effectiveness of the final medicinal product[1]. Therefore, the choice of the polymorph form for development is typically a compromise between the physical and chemical, pharmaceutical and biopharmaceutical properties of the drug.
In this study the effect of water activity, a_w, on the dehydration kinetics of the channel hydrate theophylline was evaluated. For investigation of the solvent-mediated transformation the a_w values in the crystallization media at which dehydration process ceased were determined. Then, suitable analytical techniques namely Raman spectroscopy, XRPD and microscopy, as well as Karl Fischer titration, are utilized to characterize the solid phase obtained after the equilibration of theophylline in the binary mixtures (solvent + water) for a period of one month at ambient temperature. To evaluate the obtained data multivariate statistical techniques were applied. The knowledge about the effect of a_w may be useful tool to guide the choice of the preferred physical form for substances where anhydrous and hydrated forms are known to exist.

The study was supported by Mobility Fund (FM/a/2020-2-035) and POINT program.

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PT10

FLUIDITY IN HUMAN STRATUM CORNEUM LIPID ASSEMBLY

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Unlike the lipids present in biological membranes, skin barrier lipids are rigid in nature and tightly packed in lamellar phases, providing first-line protection to the body.[1] However, how they establish such complex structures is still unknown. In our efforts to clarify such mechanisms, *in vitro* models with isolated human SC lipids have been used to study lipid arrangement. The annealing temperatures chosen were above and below the lipids' main phase transition (~ 65°C),[2] in the presence or absence of water vapor. X-ray diffraction data showed the formation of a long periodicity phase (LPP) and a cholesterol phase in all the samples while a short periodicity phase (SPP) was visible only when the lipids were annealed in a fluid state at 70°C or higher (in the presence of water vapor), or at 80°C or higher (without the presence of water vapor). Fourier-Transform Infrared spectroscopy (FTIR) showed a tighter lipid chain packing at higher annealing temperatures and an increasing trend of ordered all-trans solid-state of the lipids. Permeability studies were in accordance with the FTIR outcomes. To conclude, our data suggest that LPP was spontaneously formed without needing any fluidization of the lipid chains. Nevertheless, temporary fluidization was essential to seal nanoscopic packing defects and reduce permeability of the *in vitro* models.

The study was supported by Czech Science Foundation (19-09135J), Charles University (GAUK 1156120 and SVV 260547)

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PT11

INFLUENCE OF STEARIC ACID AND MAGNESIUM STEARATE ON FLOWABILITY AND COMPRESSIBILITY OF TABLET MIXTURE

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Lubricants are excipients added during tablet manufacturing in order to improve the flow of the bulk powder whilst additionally reducing the stickiness of tablets during compression.[1] This presentation will compare the physical characteristics and flow properties of the tableting mixture with the addition of lubricants between preparations of 0.5 % Magnesium Stearate (MgSt) and 0.5 % Stearic Acid (Ast) powders as well as comparing the properties of prepared tablets. The lubricants were blended with a mixture of Microcrystalline cellulose/Lactose monohydrate 1:1 (MCC102/L) via a sandwiching method for seven minutes using an ERWEKA 3D mixer. The particle sizes of the raw substances were measured before mixing; bulk, tapped and true density were recorded from the resulting mixtures. The mixtures were compressed and thirty tablets were produced at 3 different compression forces (5 kN, 7 kN and 10 kN) using a Zwick-Roell tableting press. The force-displacement profile and the ejection force of the tablet from the die was recorded for at least ten tablets at each force. Twenty-four hours after compression the tablets were tested using 'European Pharmacopoeia' techniques to measure friability, disintegration time and crushing force. In addition to this, the elastic expansion of the tablets was also noted. Both lubricants reduced the ejection force significantly compared to MCC102/L, the effect of Ast at compression forces 7 kN and 10 kN was lower. Tablets compressed with Ast exhibited less expansion after compression compared to MgSt. On the other hand, both lubricants prolonged the disintegration time whilst showing similar compressibility. Tablets only passed friability testing at a compression force of 10 kN.

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PT12

STUDY OF SURFACE ENERGETICS OF DISORDERED PHARMACEUTICAL SILICA

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Mesoporous silica are of great importance for poorly soluble drugs formulation [1]. Until now, there has been little research invested in the study of surface energetics of mesoporous materials and, if at all, then only for ordered silica [2]. Therefore, the aim of this study was to study surface energies of disordered pharmaceutical mesoporous silica carriers (Aeroperl® 300 Pharma, Syloid® XDP 3050 and Parteck® SLC 500). Inverse gas chromatography was used in conjunction with Nitrogen BET (Brunauer-Emmet-Teller) measurements. Results were obtained in terms of quantitative disperse and polar surface energies and as well Gutmann acid-base constants. The octane BET at room temperature was further proposed as more realistic determination of surface area for drug loading compared to the small Nitrogen molecules at - 195.8 °C (77 K) [3]. The achieved findings show pronounced differences among the used carrier materials regarding the drug accessible surface areas and surface energies that are closely related to several important physicochemical material properties like cohesion. These outcomes support the development of pharmaceutical mesoporous drug formulations.

The study was supported by SVV 260 547

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PT13

DEVELOPMENT OF FILM FORMING SYSTEMS BASED ON PLGA I

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The aim of this work is to characterize the chosen PLGA derivates plasticized with ethyl pyruvate, methyl salicylate or triacetin and evaluate their suitability for the formulation of film forming systems (FFSs), a perspective dosage form for topical application.[1] The effect of the plasticizers on the rheological and adhesive properties of the polyesters was tested.[2] All tested plasticizers decrease the viscosity of the polymers with ethyl pyruvate being the most effective. The correlation of the flow curves of the plasticized PLGA derivates to Power law and Newton models was analyzed revealing the Newtonian character of the systems. The evaluation of viscoelastic behavior showed liquid-like characteristic of these systems. The adhesive properties were determined by the tensile test providing the detachment force, time necessary for force to decrease by 90% and area under force/time curve. The highest adhesiveness was found in case of the most viscous systems. FFSs loaded with salicylic acid were prepared and their structure was studied with SEM showing the high degree of homogeneity. The images confirmed molecularly dispersed drug in PLGA previously determined by DSC. Finally, the dissolution of salicylates was tested.[3] Prolonged release of salicylates within 11 days was found with a linear pattern within first 5 days. When combined with suitable plasticizer, PLGA as well as its derivates branched on tripentaerythritol, polyacrylic acid or dipentaerythritol have adequate thermal, rheological and adhesive properties for formation of *in situ* films.

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PT14

IMPROVING THE SOLUBILITY AND DISSOLUTION RATE OF CYCLOSPORINE A BY THE LIQUISOLID TECHNIQUE

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Low aqueous solubility of drugs leads to slow dissolution rate, which can in turn result in poor bioavailability (1). This poses a challenge in obtaining suitable oral dosage forms. Thus, techniques for improving the solubility and drug release continue to be explored. Some recent approaches focus on the formulation of liquisolid systems (LSS), which are prepared by dispersing the drug in a non-volatile hydrophilic solvent and subsequently blending with selected carrier and coating materials to obtain a dry, non-adherent freely flowable powder suitable for further processing (as tablets or capsules). The drug in LSS is in a solubilized/molecularly dispersed state, and due to better wettability and higher surface area available for dissolution, higher drug release rate and bioavailability is expected (2). In this study, Cyclosporine A (CyA), was used as a model poorly soluble drug. LSS were prepared using Transcutol® HP, Polysorbate 80, Propylene glycol, Polyethylene glycols 200 and 400 as solvents and Neusilin® US2 as a carrier-coating material. The dissolution rates were monitored for 24 hours in biorelevant dissolution media – Fasted State Simulated Gastric and Intestinal Fluids (FaSSGF and FaSSIF), of pH 1.6 and 6.5 respectively. The results suggest that improved solubility and dissolution of CyA can be achieved by LSS. The highest drug release was obtained from LSS containing Transcutol as the solvent.

The study was supported by GA UK 70119 and by SVV 260 547

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PT15

IS IT POSSIBLE TO 3D-PRINT ORODISPERSIBLE TABLETS USING FUSED DEPOSITION MODELING?

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Orodispersible tablets (ODT) are characterized as tablets that disintegrate in the mouth rapidly before swallowing. The Ph. Eur.[1] requires the disintegration time within 3 min, whereas according to FDA (USP)[2], the disintegration time must not exceed 30 s. Fused deposition modeling (FDM) is a 3D printing technology with the possibility to produce small batches of customized tablets characterized by complex structures.[3] In this study, five different tablet's shapes were designed and the effect of the surface/mass ratio, the influence of excipients, and storage conditions on the tablet's disintegration time were analyzed. As model active pharmaceutical ingredients, paracetamol and domperidone were used. By combining different parameters, the tablets with disintegration time 2 min 22 s and 2 min 25 s for paracetamol and domperidone tablets, respectively, were obtained, which fulfilled the Ph. Eur. requirement. The tablet's immediate-release characteristics were confirmed during the dissolution studies with 85% of domperidone and 75% of paracetamol released within 10 min. The SEM and 3D microscopy images showed that the porous structure of these tablets was reproduced. Thus, this study demonstrated the feasibility of preparing orodispersible tablets by FDM which may expand the possibilities of its use in individual pharmacotherapy.

The study was supported by Funding Agency of Charles University under Grant SVV 260 547, and the National Science Centre (Poland), grant number: OPUS 16 No. 2018/31/B/ST8/01327.

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