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ABSTRACT BOOK

PP001

FORMULATION OF ATORVASTATIN CALCIUM LOADED CHITOSAN NANOPARTICLES BY NANO-SPRAY DRYING METHOD FOR SUSTAINED DRUG DELIVERY

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Objective
The purpose of this study was to formulate and fully characterize atorvastatin calcium loaded chitosan nanoparticles (ATR-CH-NP) by Nano-spray drying method.
Methods
ATR was dissolved in methanol and added on acidic solution of CH. Polyethylene glycol was used as surfactant to prevent precipitation of ATR. Afterwards, solution was sprayed by Buchi B-90 Nano-spray dryer. Polymer molecular weight and concertation, API concentration, nano-spray dryer nozzle inner diameter as effective variables on particle size, loading efficiency and product yield were investigated. ATR release from ATR-CH-NP was evaluated by incubating nanoparticles in 20ml phosphate buffer solution (pH 6.8) at 37°C±1°C. 1 ml sample was withdrawn at predetermined time points and analyzed by HPLC method, which is developed and fully validated. Nanoparticles were characterized with respect to morphology, particle size, polydispersity index, zeta potential and loading efficiency.
Results
The surface morphology of particles was investigated by SEM and TEM. The images indicated that, all nanoparticle formulations were spherical in shape. The surface of small particles was smoother than bigger particles. The average particle size of formulations was within the range of 510-820 nm. Zeta potential, polydispersity index and loading efficiency were ranging from 11.1±1.09 to 26.6±1.65, 0.1±0.02 to 1and 49.62±2.91 to 23.37±2.71, respectively and particle showed positive charge with homogenous size distribution. ATR showed sustained release profile for a period of 300 up to 650 hours. The nanoparticle yields considerably varied between 58.3% and 74.1%. An increase in proportions CH, ATR and spray cap resulted in an increase in product yields.
Conclusion
ATR-CH-NP was successfully prepared by nano-spray drying method with spherical shape and submicron size. It was successfully achieved that the sustained release of ATR from CH nanoparticles.
The authors would like to thank TÜBİTAK for supporting this study with the project number 115S202.

PP002

DEVELOPMENT AND PHARMACOKINETIC ASSESSMENTS OF OLMESARTAN MEDOXOMIL-LOADED SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEMS.

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Objectives

Olmesartan medoxomil (OLM) is a selective antihypertensive angiotensin-II receptor antagonist. OLM suffers from restricted permeability and limited oral bioavailability in humans (26%) for many reasons, including; its low aqueous solubility (log *P* = 4.31), uncontrolled enzymatic conversion to olmesartan (OL) and efflux by drug resistance pumps in GIT. OLM-loaded self-nanoemulsifying drug delivery systems (SNEDDS) were developed aiming to surmount such limitations.

Methods

Based on equilibrium solubility studies of OLM, ternary phase diagrams were plotted using different ratios of Capmul® MCM (oil), Tween® 20 or Cremophor® EL (surfactant) and polyethylene glycol 400 (PEG; cosurfactant). Several OLM-loaded systems (micelles and SENDDS) were developed and preliminary evaluated for PDI, particle size and zeta potential. OLM-loaded SNEDDS were further characterized for self-emulsification time, morphologic characteristics. The evaluation of the *in vitro* drug release studies involved the estimation of dissolution efficiency percentages (DE_{1h}%) and drug released percentages after 5 min (Q_{5min}%) and 1 hour (Q_{1h}%). The *in vivo* absorption studies of OL following oral administration of the best-achieved SNEDDS (F9) and Benicar® tablets were evaluated in rabbits using LC-MS/MS.

Results

Compared to OLM-loaded SNEDDS, larger droplet sizes and higher PDI values were observed with OLM-loaded micelles. With respect to droplet size (60.00 nm), PDI (0.25), self-emulsification time (13 sec), zeta potential (-14.4 mV), and dissolution parameters; DE_{1h}% (47.96%), Q_{5min}% (29.78**%)** and Q_{1h}% (66.69%), one OLM-loaded SNEDDS (F9) was selected for *in vivo* studies. Compared to Benicar® tablets, a higher C_{max}, shorter T_{max}, and larger $AUC_{(0-48)}$ were attained with (F9) in rabbits.

Conclusion

The developed SNEDDS (F9) is promising system for improving the oral absorption of OLM.

PP003

REGULATORY ASPECTS OF BIOSIMILARS IN TURKEY – DIFFERENCES TO EMA AND FDA

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Objectives

With a population of approximately 80 million Turkey is one of the biggest pharmmaceutical markets in Europe and Middle East. The fact that 6 of the 10 largest selling pharmaceutical products worldwide are biologics indicates the direction of the global pharmaceutical market towards biotechnological durgs including biosimilars. Considering this, there is no doubt that the pharmaceutical market for biosimilars in Turkey is huge. Due to the fact that Turkey is not a member of EU, the question is, which regulatory guidelines are followed for biosimilars in Turkey and what are the differences compared to the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA).

Methods

The Turkish Medicines and Medical Devices Agency (TMMDA) is responsible for the regulation of pharmaceutical products, including biosimilars, medical devices and cosmetics and is based on the Regulation on the Registration of Medicinal Products for Human Use Biosimilar Medicinal Products Guideline (Guidelines on Biosimilar Medicinal Products for Human Use).

Results

There are two main differences between TMMDA, EMA and FDA, respecively, namely the source of the reference product and the interchangeability of the biosimilar.

According to TMMDA, the reference biological product chosen for analytical, non-clinical (*in vitro* and/or *in vivo*), as well as Phase I comparability studies does not need to be particularly approved in Turkey, while EMA and FDA require the reference product to be sourced from the country/region of interest.

Another difference between TMMDA, FDA and EMA guidelines for biosimilars is that interchangeability may be allowed in the US unlike in Turkey and in the EU. Interchangeability assessment in the EU, for example in Germany, and in Turkey is left up to the physicians and/or pharmacists.

Conclusions

According to the regulatory aspects of biosimilars there are more similarities between Turkey and EMA than between Turkey and FDA.

PP004

IMPROVEMENT OF PARTICLE SIZE AND ENTRAPMENT EFFICIENCY OF NANOCARRIERS BASED IN FLEXIBLE LIPOSOMES LOADED WITH INSULIN WITH ADDITION OF PEG-2000

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ABSTRAC

PURPOSE

The objective of this research was to develop pharmaceutical nanocarrier based in flexible liposomes for insulin with presence of polymer for test by oral route, to reduce the gastrointestinal degradation and improve absorption through membranes, considering this route as the most convenient physiologically, due allow reach similar release to the endogenous secretion.

METHODS

Different percentage of PEG-2000 were added (1%, 5%, 10%, 12,5% and 15%) to conventional formulation of flexible liposome [Soy L-α-phosphatidylcholine (PC), sodium cholate (SC)] (PC 88%; SC 11%) with relative high entrapment efficiency (61.26%). All formulations were manufactured by Heating method. Z Potential, size particle, polydispersity index and percentage of encapsulation were evaluated in all formulations.

RESULTS

All formulations showed polydispersity but adequate Z potential. However entrapment efficiency improved only for the 10% PEG inclusion, reaching approximately 81,9% of enclosure of insulin. While the others formulations showed reduction in percentage of encapsulation. Integrity of this protein after preparation process was determined by Polyacrylamide Gel Electrophoresis Gel (PAGE).

CONCLUSIONS

Results showed that inclusion of polymer in the flexible liposome structure generates an excellent nanocarrier for proteins like insulin in terms of stability and composition. PAGE evaluation confirms that insulin remains complete. Nevertheless, to evaluate the biological action is necessary realize in vivo test in diabetic subjects.

PP005

POPULATION PHARMACOKINETIC ANALYSIS OF INHALED FORMOTEROL IN ASTHMA PATIENTS

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Objectives
Develop a population pharmacokinetic model able to describe the absorption kinetics and enterohepatic recirculation (EHC) of formoterol after inhalation.
Methods
Plasma concentration (C) – time (t) data of formoterol were obtained from a single dose, 2x2 bioequivalence study comparing two dry powder inhalers (DPIs) in 90 asthma patients under fasting conditions, with activated charcoal administration. Non-linear mixed-effect modeling was applied and a pharmacokinetic model able to describe the disposition kinetics of formoterol was developed. Different methodologies for the EHC of the drug were investigated. Several error models were tested, whereas the period and treatment effects, and demographic characteristics were explored as potential covariates. The entire computational work was implemented in Monolix 2016R1.
Results
Formoterol C-t profiles were best described by a two-compartment disposition model linked to bile and gastrointestinal (GI) compartments. Elimination from the central and bile compartments was considered to follow first order kinetics. The final model included an EHC loop using two additional compartments (bile and GI) linked by first order kinetics and a gallbladder emptying time interval. The model was parameterized in terms of the lung absorption rate constant (K_L), the apparent volume of distribution in the central (Vc) and peripheral (Vp) compartment, the apparent clearance from the central compartment (CL/F), the inter-compartmental clearance (Q/F), the transfer rate constant to bile (Kb), the excretion rate constant from bile to the intestine (Kg), the GI absorption (Ka) and fecal elimination (Kfec) rate constants. A combined error model led to the optimum performance. No significant covariate was found. No difference in the performances of the two DPIs was observed.
Conclusions
A population PK model with an EHC component was found to fit suitably the plasma C-t data of inhaled formoterol. Several scenarios were developed and their performance was evaluated in terms of physiological soundness and goodness-of-fit criteria.

PP006

THERMO-RESPONSIVE CHIMERIC LIPOSOMES AS INNOVATIVE DRUG NANOCARRIERS

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Objectives
The aim of this study was to investigate the physicochemical and thermotropic characteristics of chimeric liposomes, emerging from the mixing of the thermoresponsive polymer $C_{12}H_{25}$-poly(N-isopropylacrylamide)-COOH and the phospholipid L-α-phosphatidylcholine hydrogenated (Soy), at six different molar ratios. PNIPAM is an amphiphilic homopolymer, which has the ability to undergo a conformational transition, when heat is applied,due to its lower critical solution temperature (LCST) being 32°C. HSPC is a phospholipid with main transition temperature (T_m) around 52°C.
Methods
Initially, we developed conventional and mixed liposomal nanocarriers, by thin-film hydration, followed by probe sonication,in order to decrease their size. Then, we fully characterized the physicochemical behavior and stability of the mixed nanoassemblies, with light scattering techniques, while their thermotropic properties were evaluated, using differential scanning calorimetry (DSC).
Results
Conventional HSPC liposomes exhibited smaller size and polydispersity than the other prepared systems. After the incorporation of $C_{12}H_{25}$-PNIPAM-COOHat the lowest molar ratio, a gradual increase of D_h and PDI was observed, while at higher concentrations of PNIPAM, biomaterials exposed better cooperativity, leading to chimeric liposomes of smaller size and greater homogeneity. Each formulation retained its original physicochemical characteristics for a one-month period. Thermodynamic findings are in line with physicochemical results, since small amounts of polymer provoke a major perturbation in lipid bilayers, while higher molar ratios slightly alter the thermotropic behavior of pure HSPC lipid bilayers. The presence of the polymeric component plays a key role in the thermal behavior and the structural rearrangement of lipid membranes.
Conclusions
By understanding how these thermoresponsive nanotechnological systems self-assemble, we can use them as advanced drug delivery nanosystems, with controlled release properties.

PP007

SPRAY DRYING OF FLAX SEEDS MUCILAGE (LINUM USITATISSIMUM)

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Objectives
The purpose of this study was to establish the optimal conditions for spray drying of mucilage from flax seeds (*Linum usitatissimum*, *Linaceae*). Powdered mucilage can be used as a superdisintegrant in orodispersible tablets due to its ability to swell.
Methods
Aqueous extraction was carried out at 20 °C and at 40 °C and kept 48 hours for complete extraction of the polysaccharides to produce a thick viscous solution. The prepared solution was then spray dried using B-290 Büchi Mini Spray Dryer in order to obtain fine particles. The resulting powders were analyzed in terms of rheological parameters and moisture content. Particle shape and size were evaluated using light electron microscopy.
Results
The influence of spray drying conditions – inlet air temperature, feed flow rate and atomization speed on mucilage powder properties was evaluated. The main technological problem was to find the optimal inlet air temperature in order to achieve a satisfactory particle yield. Inlet air temperature of 110 ° C was determined optimum, since at 100 °C the solvent could not be effectively evaporated and at much higher temperatures as 140 °C polysaccharides sticked to the drying chamber and the cyclone of the apparatus. The feed flow rate and atomization speed had a significant impact on the particle size distribution and thus influenced powder flow properties.
Conclusion
Optimal technological parameters for spray drying of flax seeds mucilage were defined. The obtained powders demonstrated satisfactory flow properties and could therefore be used as potential excipients for solid dosage forms.

PP008

INTERACTIONS OF POLY(ETHYLENE GLYCOL-B-PHENYL OXAZOLINE) DIBLOCK COPOLYMERS WITH PROTEINS

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Objectives
The aim of the present study was to investigate the possibility of combining the properties of PEG hydrophilic segments with the ones of hydrophobic PPhOx segments.
Methods
Amphiphilic copolymers composed of biocompatible poly(ethylene glycol) (PEG) and poly(2-phenyl-2-oxazoline) (PPhOx) blocks with different molecular weights and compositions are synthesized. Their molecular characteristics are determined by size exclusion chromatography (SEC), proton nuclear magnetic resonance (1H NMR) and Fourier Transform infrared spectroscopy (FTIR). Then the self-organized PEG-b PPhOx behavior in aqueous solutions was elucidated by dynamic and static light scattering (DLS, SLS) and scanning electron microscopy (SEM).
Results
The molecular weights (Mn, Mw) are similar for the copolymers. In aqueous solutions the size of the formed aggregates is much higher than the one expected from single core-shell micelles and point to larger spherical aggregates. The aggregation state is found to be temperature-sensitive. The internal environment of these aggregates is considerably polar as evidenced by pyrene fluorescence measurements. The interactions of the synthesized diblock copolymers with fetal bovine serum (FBS) proteins are investigated and further aggregation of the initial structures are observed in the presence of serum proteins. The ability of the PEG-b-PPhOx aggregates to associate with proteins is tested also for the case of bovine serum albumin (BSA), where it is found that accumulation of BSA globules occurs.
Conclusions
PEG-b-PPhOx amphiphilic block copolymers were synthesized and their molecular structure was characterized. The copolymers were directly soluble in water where they formed spherical nanoassemblies/ aggregates which were thermosensitive. The PEG-b-PPhOx aggregates in PBS were proven to complex to some degree with the FBS proteins and BSA indicating their potential for drug delivery and protein separation applications. The studies presented here in contribute to the design and development of polymeric nanocarriers for therapeutic compounds of protein or peptide nature.

PP009

LIPOSOMAL AND NIOSOMAL NANOCARRIERS: DIFFERENCES IN PHYSICOCHEMICAL CHARACTERISTICS

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#equal contribution to this work

Objectives

Liposomes are biocompatible and biodegradable drug delivery nanoparticulate systems which are obtained spontaneously by addition of amphiphilic lipids into aqueous media. Niosomes are self assemblies of non-ionic surfactants which resemble liposomes in their structure and can be used as an attractive and alternative approach in comparison with liposomes. Niosomes are hydrated nanoparticulate systems containing non-ionic surfactants along with cholesterol or other lipids delivering small molecules and proteins to targeted site. They are biocompatible (non toxic), requiring less production cost in comparison to liposomes, physicochemically stable over a long period of time in different conditions and biodegradable. The aim of this study is to design and develop liposomal and niosomal carriers.

Methods

We used lipids with different main transition temperature (Tm) i.e 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC, Tm=55ºC); L-α-phosphatidylcholine, hydrogenated (Soy) (HSPC, Tm=52 ºC) and egg Phosphatidylcholine (EggPC, Tm=23 ºC). Niosomes were consisted of Twen-80: cholesterol (9:1 and 7:3 molar ratios) and Span-80:cholesterol (9:1 and 7:3 molar ratios). Thin film –hydration method was used as preparation protocol of all systems. Dynamic and Electrophoretic Light Scattering were used in order to elucidate the physicochemical characteristics of all systems.

Results

All liposomal systems exhibited size below the 100nm. The ζ-potential was around zero, indicated absence of surface charge in the lipid surface. The size of niosomes was strongly depended on the surfactant used. Namely, the niosomes prepared from Span 80 were in the nanoscale, while the size of Tween 80 niosomes was greater than 500nm. All niosomal formulations exhibited negative ζ-potential, but the ζ-potential values of Span 80 niosomes were extremely negative.

Conclusions

The results from this study indicated that the type of surfactants altered the physicochemical characteristics of vesicular systems.

PP010

ROLE AND TRANSLATIONAL POTENTIAL OF HYDROGEN SULFIDE IN OBESITY

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Objectives
Obesity is a chronic disease, resulting from excessive fat accumulation with a rapidly increasing incidence in western societies. Hydrogen sulfide (H_2S) is an endogenously produced signaling molecule that is synthesized by cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS) and 3-mercaptopyruvate sulfutransferase (3-MST). We investigated the role of H_2S in the development and treatment of obesity using genetic and pharmacological approaches.
Methods
Wild type (WT) and 3-MST knockout (KO) mice were fed a normal (ND) or a high fat diet (HFD) and received H_2S donor treatment (1mg/kg Na_2S i.p.). Metabolic measurements were performed using an Oxymax indirect calorimetry system. Visceral fat was used for real-time PCR, western blot analysis and histological studies. Differences were analysed by two-tailed t-test or ANOVA, as appropriate.
Results
Expression of CSE, CBS and 3-MST was reduced in visceral and brown fat of WT mice fed a HFD for 12 weeks compared to ND. To investigate the role of 3-MST in weight gain, 3-MST KO mice were used. These mice exhibited normal growth and weight gain up to 24 weeks of age. However, feeding 3-MST KO mice with HFD resulted in greater weight gain and impaired glucose tolerance, compared to WT. Moreover, 3-MST KO on HFD exhibited decreased O_2 consumption and CO_2 production. To determine the ability of H_2S to prevent obesity, WT animals on HFD were treated with the sulfide salt Na_2S. We observed that H_2S protects against diet-induced weight gain in WT mice and improves the diabetic phenotype. Moreover, the H_2S donor reduced both lipid accumulation in adipocytes and weight of visceral adipose tissue of HFD mice.
Conclusions
Taken together, our data suggest that low expression of H_2S-synthesizing enzymes is associated with obesity and that restoration of H_2S levels might constitute a therapeutic approach for obesity treatment.
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PP011

POPULATION PHARMACOKINETICS OF TOTAL EZETIMIBE IN HEALTHY SUBJECTS

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Objectives
To develop a population pharmacokinetic (PK) model for the plasma concentration data of total ezetimibe in healthy subjects.
Methods
Ezetimibe plasma concentration – time data derived from a randomized, open label, single dose, 2x2 bioequivalence study in 36 healthy volunteers under fasting conditions. Population PK modeling was applied for the description of the total ezetimibe which refers to the sum of free and conjugated ezetimibe. Several structural and residual error models were utilized and assessed. Enterohepatic recirculation was incorporated in the PK model as a secondary input into the gastrointestinal tract. Demographics (body weight, age, height, body mass index) and laboratory biochemical variables (urea, creatinine, creatinine clearance, AST, ALT, albumin, bilirubin (total, conjugated, free), and HBs Ag) were examined as possible covariates for the PK model parameters. Also, the effects of 'period' and 'treatment' were assessed for their impact on ezetimibe kinetics. Evaluation of the results relied on statistical information criteria, goodness-of-fit plots, and the rational of the derived estimates. The whole task was implemented in Monolix 2016R1.
Results
The model, which was found to describe successfully the total ezetimibe C-t data, consisted of two-compartments in which both absorption and elimination processes followed first-order kinetics. The effect of the enterohepatic effect was apparent and was modeled successfully in all three noticeable peaks. The application of a combined error model led to the best performance, while the 'treatment' and 'period' effect were not significant,
Conclusions
The population pharmacokinetics of total ezetimibe was successfully modeled using a two-compartment model joint with enterohepatic recirculation. The developed model captured all subsequent (after the maximum plasma concentration) peaks.

PP012

A Population Pharmacokinetic Analysis of Losartan

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Objectives
The purpose of this study was to apply non-linear mixed effect modeling in order to investigate: a) the pharmacokinetics (PK) of losartan and b) the contribution of various covariates aiming at the individualization of dosage regimens.
Methods
Plasma concentration (C) – time (t) data of losartan were obtained from a randomized, crossover, 2x2 bioequivalence study in which 32 volunteers received a single oral dose of 50 mg losartan. An automated LC-MS/MS method was developed for the quantitative determination of losartan in plasma. A variety of initial conditions, covariates (body weight, age, sex, height, BMI), as well as structural (one-, two-, three-compartment models) and residual error models additive, proportional, combination, exponential) were examined. Evaluation of the models was based on several criteria like the log likelihood, the Akaike and Bayesian information criteria, and the goodness-of-fit plots. The entire modeling work was implemented in Monolix® version 4.3.3.
Results
A *two-compartment model* with first-order absorption and elimination kinetics joint with a combined error model led to the optimum performance. The population parameter estimates were as following: first-order absorption rate constant was 2.18 h^{-1}, apparent clearance was 138,000 mL/h, inter-compartmental clearance (Q) was 465,000 mL/h, while volumes of distribution of the central (V_1) and peripheral compartments were 28,600 mL and 109,000 mL, respectively. Body weight showed a positive significant impact on V_1, whereas age influenced negatively the value Q.
Conclusions
A two-compartment model with first-order absorption and elimination kinetics was able to describe the PK of losartan. Weight and age influenced the values V_1 and Q, respectively.

PP013

POPULATION PHARMACOKINETICS OF ORALLY ADMINISTERED HYDROCHLORTHIAZIDE

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Objectives
To apply population pharmacokinetic (PK) modeling for the description of the hydrochlorothiazide kinetics.
Methods
Hydrochlorothiazide plasma concentration (C) – time (t) data from a single dose, 2x2 bioequivalence study in 38 volunteers under fasting conditions. Nonlinear mixed effect modeling was applied in order to describe the kinetics of hydrochlorothiazide. Several structural and residual error models were evaluated. The effects of 'period' and 'treatment' were assessed for their impact on hydrochlorothiazide kinetics. Other potential variables evaluated as potential covariates were body weight, gender, height, age, creatinine clearance, glucose levels, liver enzymes, and several other biochemical laboratory values. Evaluation of the results was based on goodness-of-fit plots, statistical information criteria, and the physiological soundness of the derived parameters. The entire computational task was performed in Monolix 2016R1.
Results
A two-compartment model with first-order absorption and elimination from the central compartment was found to describe best the C-t profiles of hydrochlorothiazide. The use of a combined error model led to the optimum results, while the volumes of distribution of the central and peripheral compartments were found to be correlated one to another. The 'treatment' and 'period' effect were not significant, whereas the role of 'age' was found to be significant. In particular, as the subjects' age increased, renal clearance was found to get lower.
Conclusions
A population pharmacokinetic model was developed for the description of hydrochlorothiazide kinetics. Age is important for the determination of the pharmacokinetics of hydrochlorothiazide.

PP014

INFLUENCE OF POLYMER CROSS-LINKING ON THE PROPERTIES OF SPRAY-DRIED CHITOSAN MICROPARTICLES LOADED WITH DOXYLAMINE AND PYRIDOXINE

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Objectives
The aim of the study was to investigate the effect of cross-linking and concentration of cross-linking agent glutaraldehyde on the properties (shape, size, entrapment efficiency, swelling and *in vitro* drug release) of spray-dried chitosan microspheres loaded with the drug combination doxylamine/pyridoxine.
Methods
Non-crosslinked and crosslinked drug-loaded chitosan microspheres were prepared by a spray drying method. Glutaraldehyde in varying concentrations was used as a crosslinking agent. The obtained microparticles were characterized in terms of shape, median diameter, particle size distribution, surface morphology and entrapment efficiency. X-ray powder diffraction (XRPD) was applied to investigate possible transformations in the solid state of the drugs. FTIR spectroscopic analysis was carried out in order to evaluate drug-polymer interactions. Drug release profiles were obtained via diffusion through dialysis membrane into phosphate buffer pH 6.8.
Results
Both non-crosslinked and crosslinked microparticles were spherical in shape. A slight decrease of the median particle diameter and the drug entrapment efficiency was observed in the cross-linked models. It was found that the increase in glutaraldehyde concentration diminished both the swelling capacity and the zeta potential of the particles. The *in vitro* drug release from the non-crosslinked microspheres was “biphasic” with initial burst release at a great rate. That intense burst effect was reduced after crosslinking the polymer with glutaraldehyde during the preparation of the microspheres and a prolonged drug release was achieved.
Conclusion
Polymer swelling and drug release rate of the drug-loaded chitosan microspheres could be modified by adding different concentrations of glutaraldehyde into the chitosan solution to be spray-dried. The formulated cross-linked particles offer sustained release of the drug combination doxylamine/pyridoxine and could therefore be a promising drug delivery system.

PP015

ANTIOXIDANT PROPERTIES OF SPRAY-DRIED LEAF EXTRACT OF *BETULA PENDULA* ROTH

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Objectives
The aim of this study was to investigate the antioxidant capacity of a dry leaf *Betula pendula* extract.
Methods
In our previous work, the dry herbal extract was prepared and characterized. Total flavonoid content was determined, applying the colorimetric method with $AlCl_3$. The antioxidant capacity of the extract was evaluated by two of the most common methods. The ability of the extract to scavenge DPPH free radicals was assessed by the method described by Brand-Williams with suitable modifications, in concentration range 5 – 80 µg/ml. 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS) decolorization assay was also applied. Antioxidant activity (% inhibition) against ABTS was measured on the 2nd, 15th, and 30th min using extract concentrations in the range 50 – 800 µg/ml.
Results
The spray-dried extract of *Betula pendula* showed a total flavonoid content of 42.5 mg/g, expressed as quercetin. DPPH scavenging activity (%I) was found to be in the range 82-99%. Results show that antioxidant activity against ABTS was extract concentration and time of incubation dependent. For example the concentration of 50 µg/ml led to 23.84 – 45.42% scavenging activity; 100 µg/ml induced an activity from 46.86 to 71.24%; and 200 µg/ml – 63.56-99.52%.
Conclusions
The results obtained from the study demonstrate the antioxidant capacity of a dry *Betula pendula* leaves extract. It exhibits a strong antioxidant activity at low concentrations. This presents the potential opportunity to prepare a natural product with high value, helpful in preventing various oxidative stress related conditions.

PP016

A TRIPHENYLPHOSPHONIUM-FUNCTIONALIZED MITOTROPIC NANOCARRIER FOR EFFICIENT CO-DELIVERY OF DOXORUBICIN AND CHLOROQUINE

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The need for specific delivery of therapeutic agents to cell mitochondria has recently attracted a lot of attention.[1] Strategies employing the use of drug delivery systems decorated with mitotropic ligands such as the alkyl-triphenylphosphonium groups (TPP) are becoming increasingly popular as they can be proven generic platforms for loading a diversity of therapeutic agents.[2] The aim of the present study is to use a novel hyperbranched polymer-based mitotropic nanocarrier for efficient delivery of both chloroquine and doxorubicin to cell mitochondria, and assay the activity of this system against adenocarcinoma cell lines. Specifically, decyltriphenylphosphonium groups (TPP) were introduced to a hyperbranched poly(ethyleneimine) (PEI) of 1300 molecular weight. Controlling the hydrophobic assembly of these macromolecules afforded ~100 nm diameter nanoparticles (PEI-TPP). PEI-TPP nanoparticles were loaded with doxorubicin (DOX) or chloroquine (CQ) or both CQ and DOX affording PEI-TPP-CQ, PEI-TPP-DOX and PEI-TPP-DOX-CQ nanoparticles of 80-100 nm average diameters. We assayed the inhibition of human prostate adenocarcinoma DU145 and PC3 cell proliferation by the MTT assay. It was found that PEI-TPP was subtoxic, DOX and CQ targeted to mitochondria is toxic to cancer cells, while, delivery of the co-encapsulated DOX and CQ by the nanocarrier (PEI-TPP) caused a significant viability decrease in both cell lines. The cellular uptake of PEI-TPP-DOX, PEI-TPP-CQ and PEI-TPP-DOX-CQ was determined by flow cytometry, while the intracellular localization of DOX was visualized by confocal laser scanning microscopy. As revealed by flow cytometry, PEI-TPP-DOX and PEI-TPP-DOX-CQ nanoparticles enhanced the cellular DOX uptake compared to free DOX. Based on the above results, we conclude that triphenylphosphonium-functionalized hyperbranched poly(ethyleneimine) can efficiently target mitochondria and co-deliver both DOX and CQ leading to significantly increased efficiency of doxorubicin at low (250 nM) concentrations.

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PP017

POPULATION PHARMACOKINETICS OF INHALED BUDESONIDE IN ASTHMA PATIENTS

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Objectives
Develop population pharmacokinetic models for the description of the absorption and distribution kinetics of budesonide in asthma patients after administration of two different dry powder inhalers (DPIs).

Methods
Budesonide plasma concentration (C) – time (t) data were obtained from a single dose, 2x2 bioequivalence study comparing two DPIs in 90 controlled or partly controlled asthma patients under fasting conditions, with co-administration of activated charcoal. Non-linear mixed-effect modeling was applied and a pharmacokinetic model capable of describing the parallel fast and slow lung absorption of budesonide was developed. Several error models were tested. The period, treatment and demographic characteristics were explored as potential covariates. The entire computational work was implemented in Monolix 2016R1.

Results
A two-compartment model with two parallel first order absorption processes (fast and slow) from the lungs was found to describe the C-t profiles of budesonide. Elimination from the central compartment was considered to follow first order kinetics. The model was parameterized in terms of the fast (Kaf) and slow (Kas) lung absorption rate constants, the apparent volume of distribution in the central (Vc/F) and peripheral (Vp/F) compartments, the apparent clearance (CL/F), the inter-compartmental clearance (Q/F), the relative fractions of dose absorbed either slowly (Rslow) or fast (Rfast) through the lungs, and the Rfast/Rslow ratio (z). A combined error model led to the optimum performance. Gender was found a significant covariate on Kas and Vp/F, with men exhibiting higher Kas and lower Vp/F compared to women. No difference in the performances of the two DPIs was observed.

Conclusions
The final model encompassed two parallel lung absorption processes, which described both the initial fast pulmonary absorption and the second slower absorption phase. This feature was attributed to the lung deposition of budesonide and the formation of fatty acid conjugated esters in the airways.

PP018

THE CONTRIBUTION OF AMPHIPHILIC AND PH-SENSITIVE DIBLOCK COPOLYMERS IN THE DEVELOPMENT OF FUNCTIONALIZED DRUG DELIVERY NANOSYSTEMS

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Objectives
This study aimed to thoroughly characterizechimeric/mixed nanosystems, composed of phospholipid L-α-phosphatidylcholine, hydrogenated (Soy) (HSPC) andtwopoly(2-(dimethylamino)ethyl methacrylate)-b-poly(lauryl methacrylate) (PDMAEMA-b-PLMA) pH-sensitive amphiphilic diblock copolymers, in various molar ratios.
Methods
Differential scanning calorimetry (DSC) was applied on copolymer-grafted bilayers, in order to assess the intramembrane biomaterial cooperativity. Based on that, chimeric nanoparticles were developed by thin-film hydration and characterized, in terms of physicochemical propertiesand colloidal stability, by light scattering techniques. Afterwards, their pH-responsiveness was evaluated, through an acidic protocol (pH=4.5). The nanosystems were also tested for their *in vitro* toxicity and finally, their morphology was studied by atomic force microscopy (AFM) and cryogenic transmission electron microscopy (cryo-TEM).
Results
The polymer-induced thermodynamic perturbation on the bilayer was discovered to be concertation and composition-dependent and while system cooperativity was higher for the chimeric nanosystems in pH=7.4, presence of the copolymer in pH=4.5 would induce membrane fluidization. Concerning liposomes, chimeric vesicles were larger, but more homogeneous, for certain polymer amounts. The biophysical behavior of the prepared chimeric nanostructures in acidic conditions would lead them to altered physicochemical characteristics, with reduced size and ζ-potential, because of the pH-responsiveness, induced by the PDMAEMA chains. Moreover, the particle nanotoxicity was also measured to be concentration and composition-dependent. Imaging techniques revealed the morphologic complexity of the liposomal membranes, with occasional existence of non-vesicular assemblies, which are probably connected with the toxicity profiles.
Conclusions
The results gathered for both copolymers and various system molar ratios reveal that there are optimum biomaterial combinations, with promising properties, that can be further exploited in drug delivery research and utilized in innovative therapeutics.

PP019

PREPARATION OF PH-INDEPENDENT EXTENDED RELEASE MATRIX TABLET OF PROPRANOLOL HYDROCHLORIDE

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Abstract

Extended release tablets offer many advantages in oral administration of medications.
This study reports the development and evaluation of controlled release propranolol hydrochloride matrix tablets.

Methodology

Matrix tablets weighing 600 mg containing 80 mg propranolol hydrochloride were fabricated by hot melt granulation method and direct compression of the granules. They contain polyethylene glycol 4000, polyvinyl acetate and eudragit RSPO in different ratios. Tablets were evaluated for their physical characterstics and drug release as well as swelling behavior.

Results

Results showed that the rate of release of propranolol hydrochloride was dependent on concentrations of polyvinyl acetate and eudragit RSPO in the formulation. Also in-vitro swelling study indicates that the tested formula has considerable swelling that follows almost zero-order pattern. Analysis of release mechanism showed that release of propranolol hydrochloride from matrix tablets fitted to Korsmeyers – Peppas model indicated an anomalous non-fickian transport suggesting that the drug release is mainly a diffusion- erosion controlled mechanism.

Conclusion

Propranolol hydrochloride can be prepared as extended- release pH independent matrix tablet using eudragit RSPO, polyvinyl acetate and polyethylene glycol 4000 by hot melt granulation technique. Sustained release of drug was achieved up to 12 hours and the release pattern follows Peppas model.

PP020

DESIGN, PREPARATION AND EVALUATION OF CHIMERIC PH-SENSITIVE LIPOSOMES INCORPORATINGDIMETHOXYCURCUMIN

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Objectives
The aim of this study was to develop chimeric pH-sensitive liposomes, composed of hydrogenated soybean phosphatidylcholine (HSPC) lipid, incorporating the block copolymerpoly(n-butylacrylate)-poly(acrylic acid) (PnBA-b-PAA) (85% content of PAA) and dimethoxycurcumin (DMC), in order to improve major problems of DMC, such as rapid metabolism and poor bioavailability. PAA block exhibits pH-responsiveness, because ofits–COOH regulative group, whichremains protonated under acidic pH, butis ionized to $–COO^-$under basic or neutral pH.
Methods
HSPC:PnBA-b-PAAbilayers were prepared at varying ratios and pH values, where Differential Scanning Calorimetry(DSC) revealed alterations oftheir thermotropic properties. Subsequently,HSPC:PnBA-b-PAA:DMCliposomes were prepared at 9:0.0:0.1, 9:0.1:0.1, 9:1.0:0.1 molar ratios and physicochemically characterized at two different pH values(4.0 and 7.4), using Dynamic and Electophoretic Light Scattering methods.
Results
Chimeric liposomes were found to retain theircharacteristics(size, size distribution and ζ- potential) over time, but only at pH=7.4, because the ionized $–COO^-$ group provides electrostatic repulsionandthe PnBA blockdecreases the membrane tension, inducing stability [1,2]. The DMC loading and the release were found to be strongly dependent onpolymer presence and DMC structural characteristics, such as tautomerism.Incorporation efficiency of DMC was altered among the different ratios.Releasestudy was also carried out at pH 4.0 and 7.4, where the prepared liposomes exhibited quite different behavior. However, release was sustained andthe percentage of DMC released was increased by the increase of polymer percentage at each molar ratio, at both pH values.
Conclusions
The incorporation of the appropriate amount of the PnBA-b-PAA block copolymer can modulate the system cooperativity, the liposomal stabilization and the incorporation/release properties of DMC, owned to pH-responsiveness of the polymeric guest.

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PP021

THERMAL ANALYSIS AND EVALUATION OF LIPOSOMAL SYSTEMS AND CLASSIC SOLID-STATE PHARMACEUTICAL EXCIPIENTS WITH FUROSEMIDE

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Objectives
To apply Differential Scanning Calorimetry(DSC) in chimeric bilayers, chimeric liposomes, and solid-state excipients with and without furosemide.
Methods
The DSC analysis is applied to: a) chimeric bilayers composed of hydrogenated soy phosphatidylcholine and poly(*n*-butylacrylate)-*b*-poly(acrylic acid)block copolymer with70% content of PAA (PNBA-b-PAA 30/70), at 6 different molar ratios (9:0.0, 9:0.1, 9:0.5, 9:1.0, 9:2.0, and 9:3.0), b) chimeric liposomes with HSPC:PNBA-b-PAA 30/70:Furosemide, at 3 different molar ratios (9:0.0:0.0, 9:0.1:0.0, and 9:0.1:1.0), c) furosemide and solid-state pharmaceuticalexcipients sodium alginate, magnesium stearate, lactose monohydrate, polyvinylpyrrolidone of 3 different types (MW: 10,000, 29,000, and 55,000), poly(ethylene oxide) of 2 different molecular weights (MW: 4,000,000 and 7,000,000), and d)mixtures of the solid-state excipientswith furosemide.Using the DSC estimates, machine-learning techniques were further applied to reveal differences in classification of the 'a' – 'd' media.
Results
In chimeric bilayers, as the molar ratio PNBA-b-PAA 30/70 is increased, a broadening of the peaks and appearance of shoulders becomes apparent. Chimeric liposomal systems are characterizedas 'fluid-like' by their thermograms, which may be potentially translated as an easy way of release of the furosemide from the advanced delivery system. Concerning the solid-state pharmaceuticalexcipients and furosemide, their thermal behavior matcheswith that reported in theliterature. Regarding the mixtures of the excipients-furosemide, their DSC scansappear as fusion of the thermal behavior of each excipientindicatingstability over time.
Conclusions
The application of DSC scansled to information about the cooperativity of materials, thermal stability, polymorphism, and the presence of impurities in the mixtures. This information facilitates the development of safe and effective pharmaceutical formulations.

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PP023

OH-IRMOF-16 AS POTENTIAL DRUG CARRIER FOR GEMCITABINE DELIVERY. A DFT STUDY.

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Abstract
The unique physical and chemical characteristics of Metal Organic Frameworks (MOFs) make them promising candidates for drug storage and drug delivery. MOFs are organic – inorganic hybrid materials made of metal ions or clusters interconnected through an organic linker. In order to develop new and much-improved drug delivery regimes for the anticancer agent gemcitabine, the interaction of gemcitabine with the strategically modified organic linker from IRMOF-16 (non-toxic, high-loading MOF) has been investigated by employing DFT methods (PBE/TZVP). The introduction of a hydroxyl group in the organic linker of IRMOF-16 was critical for gaining key acid-base and hydrogen-bond interaction sites. The maximum interaction energy with gemcitabine was found to be 24 kcal/mol for the modified IRMOF-16. Semi-empirical calculations (PM7) were also performed in order to study the interactions of gemcitabine with larger fragments of the modified IRMOF-16 unit cell.
Keywords*: Metal-Organic Frameworks, gemcitabine, DFT methods, PM7 calculations, drug delivery*

PP024

CHEMOINFORMATICS APPROACHES FOR THE DISCOVERY OF PAN-VIRAL INHIBITORS

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Positive-strand RNA (+RNA) viruses are the largest group of human pathogens, including life-threatening infections such as hepatitis C or SARS, emerging tropical diseases such as Dengue or Chikungunya fever and ubiquitous infections such as the common cold or gastro-intestinal infections. Such viral infections are a major burden to public health and for by far the most of these viruses, no vaccines or direct acting antiviral treatments are available. As viruses make extensive use of host mechanisms for their own benefit it is important to focus on host cell processes as targets for antiviral treatment and establish a strategy for the development of true "antivirotics"– drugs that, analogously to antibiotics (effective only against bacterial infection), can be used to treat viral infections caused by a whole group of different viruses.

The most efficient, broadly active anti-viral targets or combinations of targets, and strategies to interfere with these target mechanisms to treat the infection are identified by the SysVirDrug project. We have established host cellular factors and processes, that are highly likely to sensitively influence the replicative capacity of the investigated viruses (HCV, DENV, CV, CHIKV and SARS-CoV). In this context, cheminformatics approaches are used to identify suitable drug molecules targeting the identified host cell processes. In silico tools are developed to identify commercially available potential inhibitors included in existing chemical databases (e.g. PubChem, ZINC, CheMBL, Maybridge). Docking studies, data mining and similarity techniques are combined in custom made chemoinformatics workflows with the primary objective of identifying the most promising candidates for biological screening. In iterative cycles, after experimental validation, predictions will be improved upon feedback on the biological activity, and functional inhibitors will then be structurally optimized to further increase their antiviral potential and decrease their toxicity.

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