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Faculty of Pharmacy

University of Szeged

I. Symposium of Young Researchers on Pharmaceutical Technology, Biotechnology and Regulatory Science

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Schedule

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OP-2 – 09:00-09:15 **Mahwash Mukhtar,** Rita Ambrus
Fabrication of pulmonary formulations containing hyaluronic acid and chitosan-based nanoparticles for drug delivery in tuberculosis

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OP-4 – 09:30-09:45 **Fakhara Sabir,** Ildikó Csóka
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OP-12 – 11:45-12:00 **Yousif H-E. Y. Ibrahim,** Tamás Sovány, Géza Regdon jr.
Design and characterization of Chitosan/citrate films as suitable multifunctional coating for oral -macromolecule delivery

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Development of sodium hyaluronate-based formulations loaded with nanosuspension for nasal delivery of loratadine: Simplicity of preparation and application

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OP-19 – 14:30-14:45 **Péter Gieszinger,** Rita Ambrus, Piroska Szabó-Révész
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Abstracts

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OP-1

DOI: 10.14232/syrptbrs.2019.op1

Examination of penetration through the skin by passive and active methods

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From the point of view of pharmaceutical technology, transdermal administration is an extraordinary challenge. Throughout the development of pharmaceutical technology, considerable attention has been focused on the delivery of active ingredients through the skin. However, the penetration is limited, which inhibits the optimal bioavailability of the formulations. The greatest barrier to drug entry is the stratum corneum [1]. With different technological tools like passive and active methods, the conditions of access can be optimized. Choosing the appropriate carrier systems can be a critical point in the development of the effects of the compositions. Drug carrier systems (hydrogel, oleogel, nanostructured lipid carrier, and lyotropic liquid crystal) were formulated. The effect of carrier systems was also studied in combination with electroporation. This treatment is an active method with high-voltage impulses which accelerate drug penetration through the skin [2]. Comparing the different carrier systems, the nanostructured lipid carrier was the best in both hydration and transepidermal water loss. In combination with electroporation treatment, the moisturizing effect of the carrier systems was significantly improved, which was the most successful in case of hydrogel.

The aim of further research was to detect the effect of electroporation with another method. Leica DM6 was applied to detect the penetration of label dextran of different molecular weight into different layers of the skin.

The film forming systems were a promising choice for dermal preparations [3]. Further aim of the study is the development of a formulation of a topical application.

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Acknowledgements

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OP-2

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Fabrication of pulmonary formulations containing hyaluronic acid and chitosan-based nanoparticles for drug delivery in tuberculosis

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Tuberculosis is the second most fatal disease in the world which is caused by Mycobacterium tuberculosis (MT) [1]. Different therapeutic regimens have been used in the past but drug resistance always led low patient compliance. As the bacteria resides inside macrophage during the disease phase, so developing a drug delivery system containing nanoparticles which can directly target the causative organism inside macrophage can prove to be the modern day anti TB therapy [2]. Various routes of drug administration have been explored using nanoparticles in the past but pulmonary route proves to be the most promising one [3, 4]. During nanoparticle formulation comprised of Hyaluronic acid (HA) or Chitosan, core can serve as a reservoir for various drugs for targeting macrophages in TB. Chitosan is mucoadhesive in nature and HA has an affinity for the macrophage, so these are the biodegradable polymers of choice [5]. Amoxicillin and various other drugs will be compared in terms of efficacy for reducing the symptoms of TB. Physicochemical tests including FT-IR, DSC, TGA, XRPD, SEM, size analyses and aerodynamic characterization can provide useful data about compatibility and stability of the nanoparticular system. Ex Vivo Drug Accumulation Studies on Cultured Alveolar Macrophages and stability of the formulation in Broncheo-Alveolar Lavage Fluid can be performed prior to the in vivo testing in Guinea pigs. Inhibition of bacilli growth in macrophage can reduce the production of pro inflammatory cytokines and chemokines.

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OP-3

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Basic research methods in the development process of the liposomal formulations

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Probably there would not have been any other era when alternative routes for drug administration or new therapeutic and diagnostic options had as an important part in the pharmaceutical researches as nowadays. Liposomes, a type of nano-carrier systems used for targeted drug delivery are in the centre of the up-to-date nanotechnological investigations [1].

The objectives of this research are the creation and the investigation of formulations made from different phospholipid contents, the incorporation of different types of active pharmaceutical ingredients (APIs) into the vesicles, and the study of the effects when various production methods and parameters are applied.

The first formulations were prepared by the thin-film hydration method [1]. The ratio between the phospholipids and the cholesterol were changed in addition to the temperature, the pressure, and the filtration. The size of the produced particles was determined via dynamic light scattering technique. The zeta potentials were verified to check the charge of the vesicular surface. Furthermore, thermogravimetric analyses and spectrophotometric measurements were done. Fourier-transform infrared and Raman spectroscopies, moreover, small-angle X-ray scattering measurements are planned to be done in the close future.

Most of the liposomal formulations were prepared with vesicles under 100 nm from different combinations of wall contents. The measured zeta potential values were slightly negative except the API-containing formulations.

We would like to prepare and study further liposomal formulations and broaden the scale of the used APIs and the techniques of the production.

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OP-4

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Exploiting potential of intranasal delivery of lipid nanoformulation for targeting glioblastoma

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Malignant gliomas are most devastating and deadly forms of tumors. Prolonged exposure of gliomas with high concentration of anti-cancer drugs is pre-requisite for therapeutic efficacy. But there are several limitations depending upon physiochemical characterization of the compound and impermeable nature of blood brain barrier (BBB) often results in sub-therapeutic drug concentration. Blood brain barrier is the major problem in drug delivery to the brain. In gliomas microvasculature exhibits physiological characteristics quite distinct from the intact cerebral structure. Second part of the review consist the use of non-invasive strategies to circumvent the BBB and deliver drug into the brain. Intranasal delivery route is the most suitable non-invasive route and it has the advantage of by passing the BBB and large number of compounds can reach the brain directly through various passages. Lipid-nanoformulations like liposomes and solid lipid nanoparticles have been largely exploited for brain targeting can be the most suitable carrier for gliomas. This review summarizes the introduction of glioblastoma, barriers to brain delivery, best carrier system for intranasal delivery and mechanism in drug transport to the brain for targeting glioblastoma.

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OP-5

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Preparation and investigation of levodopa-containing powders for alternative administration

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Levodopa (LEVO) is the most widely used active pharmaceutical active agent in the treatment of Parkinson's disease. During the per os administration, the significance of off-period increases, therefore it is necessary to find additional therapeutical possibilities. Nasal delivery of levodopa can be a suitable choice.

Nasal powders were prepared as a binary system with excipients by a dry co-grinding process. The co-grinding process parameters (LEVO:excipient ratio and grinding time) resulted the 5-40 µm particle size range. The co-grinding process decreased the degree of crystallinity of LEVO. The α-cyclodextrin and PVP had an intensive crystallinity degree reducing effect. HPMC, PVP and D-mannitol associate around the LEVO crystals preventing its crystalline structure. Presence of hydrogen bond was detected only for LEVO-PVP and LEVO-D-mannitol. Chemical degradation of LEVO in the binary ground systems was not detected. The dissolution rate of the products was controlled.

Besides nasal powders composed of levodopa and chitosan or sodium hyaluronate[1] were also prepared with a planetary ball mill. The rotation speed, the milling time and the drug-excipient ratio were evaluated to be the most relevant milling factors - as a result of the initial risk assessment according to a factorial design. Milling in the presence of higher amount of sodium hyaluronate resulted in smaller average particle size of powders and higher initial dissolution and permeation of LEVO compared to chitosan-containing formulations.

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Acknowledgement

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OP-6

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Nanocarrier Based Systems for Nose to Brain delivery of Anti-Neurodegenerative Medicines

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As the prevalence of the neurodegenerative diseases is steady increasing and most of the patients are elderly people, discovering and formulating effective, easy-to- use and non-invasive therapies are two of the main goals of pharmaceutical technology and regulatory affairs. In the presence of the blood brain barrier just few medications show good penetrating and effectiveness, especially that this barrier has specific properties suit only the lipophilic and very tiny particles. Nowadays, targeted Nano therapies greatly draw attention as new possible ways to deliver medicines showing promising approach to improve their therapeutic index while reducing their side effects. Nose-to-brain as a way of delivering medicines considers one of the most recent routes shows fast and effective action and by applying lipid-based Nano-systems, the chance of obtaining the required penetration and optimum properties can be raised up, so here we discuss the types of lipid based Nano-systems, their properties, advantages and disadvantages that made them preferable as careers for nose-to-brain delivery application of some therapies targeted neurodegenerative disease.

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OP-7

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Improving the ophthalmic bioavailability of steroidal anti-inflammatory drugs

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A huge amount of the ophthalmic formulations on the market are eye drops and ointments thanks to their simple administration. Unfortunately, these formulations have very low bioavailability. Steroidal anti-inflammatory drugs are lipophilic drugs; they dissolve very poorly in water. The water solubility can be improved with cyclodextrins (CD).

The aim of this work was to combine the advantages of CD and a mucoadhesive thiolated polymer, thiolated poly(aspartic acid) (PASP-CEA) by the chemical immobilization of CD onto PASP-CEA. The formation of the CD-drug complex in the gels was analyzed by X-ray powder diffraction. The ocular applicability of the polymer was characterized by means of physicochemical, rheological and drug diffusion tests. Osmolality, refractive index, and pH were measured in aqueous solutions of PASP-CEA and PASP-CEA-CD [1].

The X-Ray diffractogram of the formulations showed an amorphous pattern. The osmolality, pH and refractive index of the polymer solution confirmed the ocular acceptability of the formulations. During the rheological investigations, the PASP-CEA solution displayed a fast solution-to-gel transition in the presence of an oxidant. The immobilization of MABCD on the polymers did not hinder the gelation process. The complexation of PR with CDs improves PR solubility in aqueous medium. The complexes diffuse in the formulation and can carry the PR molecules through the aqueous mucin layer [2]. The PASP-CEA-CD-PR complex prolonged the drug diffusion through synthetic and improved it through amniotic membrane [3].

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OP-8

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Optimization of the production process and product quality of titanate nanotube-drug composites

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Conventional drugs often have poor pharmacokinetics and biopharmaceutical properties[1]. Whereas, nanosized drug delivery systems may prolong shelf-life and enhance bioavailability and acceptability by increasing either uptake efficacy or patient compliance [2].

TNTs were synthetized with hydrothermal method, and then composites were formed with atenolol (ATN) and hydrochlorothiazide (HCT) using various solvents. Ethanol, methanol and 0.01M HCl solution or ethanol and 1M NaOH solution were used to produce TiATN and TiHCT composites respectively. The physicochemical properties of the samples were investigated by using TEM (FEI, OR, USA) and SEM (Hitachi, Japan) imaging to analyze the texture, optical contact angle tester (DataPhysics, Germany) to determine the surface free energy, FT-IR spectrometer (Thermo Fisher Scientific Ltd., MA, USA) and DSC/TG apparatus (Mettler-Toledo Ltd, Hungary) to detect the interaction between drugs and TNTs.

The results revealed that the strength of interactions is highly connected to the solubility of the drug in , and to the volatility of the applied solvent. Moreover, the strength of interactions exhibited considerable influence on the surface characteristics of the products, which determines their processability and their behaviour in biological environment.

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OP-9

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API – excipient interactions in non-biodegradable solid matrix systems

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Solid dosage forms are still the most preferred types of medicines in the pharmaceutical market. Due to the emerging trend on personalized medicine, pharmaceutical industry faces a new challenge on providing matrix systems with tailorable properties. To fulfil this request a novel approach of pharmaceutical design may be applied with a more detailed investigation of physico-chemical property-based interactions between the drug and the applied excipients. The main aim of this research work is the better understanding of these interactions and fulfilling the requirements of the 'Functionality related properties of materials' concept of Quality by Design.

A line of chemically similar APIs and matrix forming agents were mixed and directly compressed with an instrumented IMA Kilian SP300 tablet press. The interactions formed within tablets were studied by FT-IR and NIR spectroscopy, and a custom-made device was used to perform dissolution tests to obtain information about the effects of interactions on the drug liberation kinetics.

The spectral information revealed that hydrogen bonds are being formed between the drug and excipients even in solid state, while investigations during dissolution tests have proven that the strength of interactions have increased due to the formation of polyelectrolyte complexes which affects not just the speed of drug liberation but also the quantity of the liberated drug.

According to the findings it can be concluded that in addition to the physico-chemical properties of the drug delivery system, the drug liberation is fundamentally influenced by the chemical interactions formed between APIs and excipients.

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OP-10

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Design and development of a novel modified anti-microbial peptide (AMP) formula: evaluation of different parameters and risks influencing AMP effectiveness

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Antimicrobial peptides (AMPs) are small and diverse peptides which were isolated and developed due to the increasing resistance to conventional antibiotics [1]. In this work, we focused on most recently published researches that provide us with good knowledge in structural features, mechanism of action, therapeutic aim, advantages and limitations, chemical modification approaches and carrying strategies of AMPs. This gave an idea of the most effective structure and other desired physicochemical features of AMPs with the best performance to combat pathogens. In addition, recently published papers on different modification strategies and carrier systems further narrowed and specified our knowledge, and directed us on appropriate strategies in designing a high quality modified AMP formula with the most influence on bioavailability and antimicrobial activity enhancement. After performing the selected modification method of AMP, all the risk factors that influence the quality of AMP will be determined within the Quality by Design framework. The confirmation of successful modification will be performed by different physicochemical methods and followed by evaluation studies of antimicrobial activity of peptide. The final step is formulation of AMP in solid dosage form which again will be followed by an Ishikawa diagram for illustrating the factors affecting the quality of an AMPs containg drug delivery system [2].

References

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OP-11

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Skin penetration investigational methods

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The number of dermal formulations has increased in recent years. Topical semi-solid products are complex formulations with complex structure. Clinical human skin tests give the most relevant information, however, because of its high cost, it is advisable to choose simpler methods in the early stages of preparation development. Modelling of penetration through the skin is a complex challenge. Not only the device and the membrane, but also the properties of the product itself influence how the particular system can be most effectively tested. The released amount of active ingredient in vitro is an important quality attribute of the products. The diffusion and penetration of drug from different carrier systems can be studied with many types of equipment. In my PhD work, different in vitro drug release methods have been used. Two types of vertical Franz diffusion cell are tested with 3 different membranes and the Skin-PAMPA method, too. Based on our results, cellulose membranes can be used to study the drug release only. For modelling the skin penetration we should use other membranes. My further aim is to optimize the in vitro tests for modelling the human skin penetration.

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OP-12

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Design and characterization of Chitosan/citrate films as suitable multifunctionalcoating for oral-macromolecule delivery

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Nowadays, biopharmaceuticals are usually used parenterally since their oral delivery may require protection from degradation in the GI tract and enhancement of permeation and absorption [1,2]. Chitosan may isolate macromolecules from the degradation and form a matrix with the glycoproteins of mucus [3]. In addition to its mucoadhesive property, chitosan can control the drug release [4]. Citric acid (CA) can be used as protease inhibitor and as permeation enhancer [5]. The aim of this work was to formulate and to characterize chitosan citrate films.

Chitosan was used as film forming polymer, CA as solubilizing agent and glycerol, propylene glycol or polyethylene glycol were serve as plasticizers. Mucin was used as reagent for mucoadhesivity tests. Films were prepared by dissolving chitosan (2% w/v) with CA (2.5-7 w/v %) by solvent casting method. A screw micrometer (Mitutoyo, Japan) was used to measure the thickness of films, while, hardness and mucoadhesive properties were measured with a laboratory constructed texture analyzer. FT-IR spectra were obtained by an Avatar 330 (ThermoScientific, USA) apparatus and surface free energy was measured indirectly by an optical contact angle-measuring apparatus (OCA20, DataPhysics, Germany).

The results revealed that beside other effects CA also exerts a considerable plasticizing effect, which makes possible to simplify the applied formulations.

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OP-13

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Formulation and investigation of novel, carrier-based dry powder inhalation system

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Administration of the drug via the lung has several advantages in the treatment of lung diseases, such as cystic fibrosis and chronic obstructive pulmonary disease. Thus, the development of dry powder systems (DPIs) containing antibiotic [1] and non-steroidal anti-inflammatory [2] agents is on every account warranted. In the case of development, it should be borne in mind that the active ingredient particles have a good morphology and low density, between the average particle size of 1-10 µm and the cohesion between the particles is as small as possible. Furthermore, the product must have adequate stability and be compatible with the used inhaler and capsule. The aim of this work is to produce and investigate an antibiotic-containing novel, carrier-based DPI system, that combines the advantageous behaviours of traditional, carrier-based; and carrier-free DPI systems with the use of a combined formulation technique [3]. The studies show that the combined formulation has favourable physical properties, high lung deposition (*in vitro*, *in silico*), it is compatible with the used capsule (high emitted fraction) and stable.

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OP-14

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Development of sodium hyaluronate-based formulations loaded with nanosuspension for nasal delivery of loratadine: Simplicity of preparation and application

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The unique requirement for delivery of poorly-water soluble drugs has driven a great deal of research into new formulations and routes of administration. Loratadine (LOR) is a H_1 antihistamine drug. It is commonly prescribed for treatment of various allergic conditions. According to BCS, LOR is classified as class II drug. Furthermore, LOR exhibits a pH-dependent solubility. Consequently, oral administration of LOR is associated with variable and poor bioavailability [1]. Moreover, the oral administration of LOR can produce several side effects, including hepatotoxicity, and breathing exertion. Thus, alternative routes of administration such as nasal could be advantageous to overcome these effects [2].
Simple methods were used to prepare the nasal formations (NF). The nanosuspension was prepared by ultrasonication precipitation. The concept of Quality by design (QbD) was followed to link the critical process parameters (CPPs) with the required critical quality (CQAs) attributes and risk assessment to select the optimized CPPs for the preparation of the nanosuspensions that were further formulated into NFs using sodium hyaluronate (Na-HA).
The nanosuspension displayed a particle size of 311.55 nm. The NFs showed an enhanced viscosity and mucoadhesive properties. The diffusion was achieved within 1h. The NFs showed a drug and Na-HA dependent diffusion. The formula that contains of 5 mg/ml Na-HA and 2.5 mg/ml LOR showed the highest flux, and permeability coefficient.

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Novel ophthalmic formulations to increase the efficacy and stability

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The efficient therapy in ocular diseases is limited by the physiological barriers and defensive mechanisms of the eye. To reach the proper therapeutic effect, development of novel ophthalmic formulations is necessary with increased drug permeation and retention time on the surface of the eye.

Cyclodextrin (CD) derivatives are commonly used as additives in different pharmaceutical products. CDs can form water-soluble inclusion complex with lipophilic active ingredients, thus the increased penetration and improved stability of the dissolved drug are expected [1].

In this work eye drop formulations were developed with increased efficacy and stability. All formulations were set to the required parameters, which meet the physiological parameters of eye. Firstly, cyclodextrin derivatives were used to enhance the efficacy of the anti-inflammatory prednisolone by formation of water-soluble inclusion complex. To increase the retention time of this formulation, mucadhesive antimicrobial polymer was applied. The drug-cyclodextrin complex formation, the diffusion of prednisolone, surface tension, viscosity, mucoadhesivity and the antimicrobial stability of the eye drops were investigated by different methods [2]. The cytotoxicity and drug permeation were studied on human corneal epithelial cell lines. In the second main part, the stability of antibiotic, rifampicin containing eyedrops was enhanced by cyclodextrin inclusion complex and freeze-drying method. The stability of the rifampicin-cyclodextrin complexes and freeze-dried samples was investigated at different circumstances and time periods by HPLC. The residual moisture and reconstitution time were also studied.

According to the results, this work can be an innovative approach to develop ophthalmic formulations with increased efficacy and stability.

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Lipid-based delivery systems for periodontitis treatment

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Periodontitis is a chronic inflammatory disease induced by anaerobic bacteria. It is affecting tooth supporting tissues and without proper treatment it may lead to tooth loss.

Oral administration of antibiotics may not provide adequate drug levels in the periodontal pockets to eliminate microorganisms and could also lead to serious side effects, while the administration of local delivery systems containing antibiotics could help eliminate the disease [1].

The aim of the present work was to develop a swellable, biodegradable, biocompatible, mucoadhesive lipid-based local delivery systems containing antibiotics for the treatment of periodontal disease.

Lipid-based systems may be able to protect the active ingredients from environmental hazards; thus decomposition, while providing sustained release. Incorporated polymers may help the swelling and degradation; therefore, the drug release and the elimination of the delivery systems [1].

During the formulation period, different methods were used to determine the optimal composition of the lipid formulations. DSC, consistency, wettability, swelling and degradation, drug release measurements and an antimicrobial study were carried out.

Results of the different measurements and investigations show that formulations with optimal composition could provide sustained drug release and a long-lasting antimicrobial effect against periodonthopathogenic bacteria.

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Development of anti-counterfeiting protection by laser technology,

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Counterfeiting of drugs is a real threat to public health. Substandard and falsified medicines also cause serious social and economic damage. According to the new reports from WHO (2017), in the low- and middle-income countries the failure rate of these medical products is approximately 10.5% (1, 2). This global problem is on the rise, particularly on the Internet where, more than 50% of drugs could be fake (3).

According to the directive 2011/62/EU to protect the pharmaceutical supply chain from falsified drugs, unique identification should be print on the packaging of prescription medicines (2). Our team is working on the technology to develop an individual traceability 2D code directly on the surface of the tablet. Patients with a mobile phone and installed suitable application should be able to authenticate these drugs.

Tablets were coated by HPMC and PMMA polymers. For marking tablets different types of lasers were used: ArF excimer laser, semiconductor laser and Nd: Yag laser. After marking polymer films, we made an analytical quality control of them to check if there occured any change during the laser intervention, by SEM, Raman, Thermogravimetry and Mass spectrometry.

It was found out that excimer laser could be the right instrument for marking unique code on tablets against counterfeiters.

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Quality by Design driven development of Liraglutide loaded nanocarrier system designed for oral delivery

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Since Liraglutide, a fatty acid modified glucagon like peptide -1 (GLP1) analog, is still administered parenterally, this work aims at designing and optimizating Liraglutide encapsulated in polymeric nanoparticles for oral administration implementing Quality by Design (QbD) concept from the early stage of development.

Rish assessmnet based study was successfully conducted followed by selecting the crtical process parameters (CPPs) and crirtical material attributes (CMAs) with the highest risk to be further investigated applying screening design of experiment (DOE). Plackett Burman DOE was sucessfully implemented to understand and evaluate the effect of CPPs and CMAs on the size, encapsulation effeciency, polydisperisity index and zeta potential of Liraglutide loaded polymeric NPs. The design space was established and the optimized formula was prepared and examined for physiochemical properties, compatibility, structural stability and in vitro relesae behaviour.

This work presents the potential of implementing the QbD methodology when designing such a complex system to ensure high quality of the final product.

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Nasal formulation of active ingredients to induce systemic and central nervous systemic effects

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Nasal drug delivery has become one of the most researched alternative drug administration route in the last decades. The reason of the increasing interest is, that due to the unique anatomical and physiological properties, local, systemic and direct Central Nerve System (CNS) effects are available via nasal administration. In the case of therapies (e.g. CNS diseases, brain tumors), where the point of attack is in the brain, nasal drug administration can improve the efficiency of the treatment. Powders have some favourable physicochemical properties over liquid formulations, so in some cases they are preferred dosage forms [1]. Reducing the particle size to the nano range is also a common way to modify the properties of a drug and can affect its bioavailability in a positive way [2]. The aim of this research is to formulate and develop one or more alternative dosage forms for lamotrigine (LAM), that is a BCS II. antiepileptic drug and only available on the market in tablet form [3]. Since the beginning a nanosized LAM containing nasal powder has been produced, the process of sample preparation has been optimized and the samples were tested *in vivo* [4].

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Formulation of a solid oral drug delivery systems containing nanosuspension produced by combined wet milling technique

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Nanonization is a proven effective strategy to enhance the dissolution rate of poorly water-soluble drugs such as BCS class II (poorly soluble and good permeable) and Class IV (poorly soluble and poor permeable) pharmacons, thus their bioavailability can be improved [1]. To overcome the instability of the nanosuspensions and also to improve the patient compliance could be the transformation of the product into solid dosage form. In this case it is necessary to ensure the rapid dissolution characteristics of the nanoparticles [2].

Our aims were, to optimize a combined wet milling process, and to formulate solid dosage forms for oral drug administration with rapid dissolution characteristics. The formulation processes were manual granulation, fluidization and lyophylisation.

Meloxicam (Mel) was used as a model active pharmaceutical agent. During the wet milling process aqueous PVA solution was used as the stabilizing agent. The additives used in formulation processes were Avicel, Kollidon, Aerosil, Mannitol, Comprecel and Trehalose.

The optimisation process was successfully executed. The granules produced by manual granulation showed sustained release. The lyophilisates and the granules made by fluid bed granulation had rapid dissolution characteristics.

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