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

23-24 January, 2020
Szeged, Hungary

Book of Abstracts

University of Szeged

Greetings

On behalf of the Scientific Committee, I am very pleased to welcome the participants of the 2nd Symposium of Young Researchers on Pharmaceutical Technology, Biotechnology and Regulatory Science. Special greetings to the young researchers who report on their PhD work at this event.

The symposium series launched last year is a new initiative of the Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged. The aim of this program was to get to know the work of Hungarian and international PhD students working at the institute, to master the basic rules of presentation and discussion. Early acquisition of this knowledge/skills is extremely important for mobility programs, conferences, publications and later for defense of theses.

The successful 1st Symposium gave us the idea to invite our cooperative partners to participate in the 2nd Symposium. We are delighted to welcome 16 PhD students from Serbia, Romania, Czech Republic, Bosnia-Herzegovina and Slovenia.

The Symposium provides a good opportunity to meet the cooperative partners, to discuss the new developments and the future directions of the pharmaceutical sciences.

I am pleased that 70 colleagues will participate at this symposium. The program includes 1 plenary lecture and 39 oral presentations.

I am looking forward to having a successful conference with fruitful discussions and a nice time at Szeged.

Prof. Piroska Szabó-Révész
Head of Scientific Committee

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II. SYMPOSIUM OF YOUNG RESEARCHERS ON PHARMACEUTICAL TECHNOLOGY, BIOTECHNOLOGY AND REGULATORY SCIENCE

23-24 JANUARY 2020

SZEGED
Hungary

General Information

Date: 23-24 January 2020

Location:

Registration: Faculty of Pharmacy, University of Szeged
(6 Eötvös street, Szeged, Hungary, H-6720)

Symposium: Department of Rector's Office, University of Szeged
(13 Dugonics square, Szeged, Hungary, H-6720)

Congress Topics: Pharmaceutical technology, biotechnology and regulatory science

Oral presentations (10 min) followed by discussions (5 min)

DOI: 10.14232/syrptbrs.2020.af

Edited by: Tivadar Bíró

Photos by: Tamás Sovány

President of the Symposium

Ildikó Csóka

Organiser

University of Szeged, Institute of Pharmaceutical Technology and Regulatory Affairs

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Short-Programme

Thursday, 23rd January

Registration (Institute of Pharmaceutical Technology and Regulatory Affairs)

10:00 - 11:30 Registration, visiting the institute and welcome reception

Oral presentations (Department of Rector's Office)

13:00 - 14:30 **Opening ceremony and plenary session**

14:30 - 15:00 Break

15:00 - 16:45 **Section 1.**

16:45 - 17:00 Break

17:00 - 18:30 **Section 2.**

19:30 - Networking event

Friday, 24th January

Oral presentations (Department of Rector's Office)

09:00 - 10:45 **Section 3.**

10:45 - 11:00 Break

11:00 - 12:30 **Section 4.**

12:30 - 13:45 Lunch break

13:45 - 15:30 **Section 5.**

15:30 - 15:45 Break

15:45 - 17:30 **Section 6.**

17:30 - 17:45 **Closing Remarks**

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

January 23-24th 2020. Szeged, Hungary

Schedule

Thursday, 23rd January

10:00-11:30 Registration and visiting the Institute (Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged, 3rd floor, 6. Eötvös street, Szeged, H-6720)

Oral Presentations (Department of Rector's Office, University of Szeged
13 Dugonics square, Szeged, Hungary, H-6720)

13:00-14:30 Opening ceremony and plenary session

14:30-15:00 Break

15:00-16:45 Section 1. – Chairs: Prof. Dr. Edina Vranić, Dr. Géza Regdon jr.

OP-1 – 15:00-15:15 **Tivadar Bíró,** Zoltán Aigner
In vitro and *ex vivo* investigation of steroid containing ocular drug delivery systems

OP-2 – 15:15-15:30 **Jelisaveta Ignjatović,** Sandra Cvijić, Jelena Đuriš
Spray vs freeze-dried solid lipid microparticles: Challenges in development

OP-3 – 15:30-15:45 **Péter Gieszinger**, Rita Ambrus, Piroska Szabó-Révész
Formulation of nasal drug delivery systems to induce systemic and central nervous systemic effect

OP-4 – 15:45-16:00 **Juraj Martiška**, Eva Šnejdrová, Milan Dittrich
Formulation of medicated nanoparticles based on branched PLGA

OP-5 – 16:00-16:15 **Attila Léber**, Erzsébet Csányi, Mária Budai-Szűcs
PLA-based nanofibrous systems for the treatment of periodontal disease

OP-6 – 16:15-16:30 **Ivana Kurcubic,** Jelena Đuriš
Influence of experimental model, active substance and polymer type on mucoadhesive properties of buccal tablets

OP-7 – 16:30-16:45 **Cristina Barbălată**, Alina Porfire, Anca Cherfan, Felicia Loghin, Ioan Tomuță
QbD development of a liposomal co-formulation with Doxorubicin and Simvastatin for an enhanced antiproliferative effect on T47D-KBluc cell line

16:45-17:00 Break

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

January 23-24th 2020. Szeged, Hungary

17:00-18:45 Section 2. – Chair: Prof. Dr. Ioan Tomuţă, Dr. Erzsébet Csányi

OP-8 – 17:00-17:15 **Merima Sirbubalo**, Amina Tucak, Edina Vranić, Andreas Zimmer
Stearylamine-based nanoemulsion: preparation, characterization and physical stability investigation

OP-9 – 17:15-17:30 **Ruba Ismail**, Ildikó Csóka
Potential of polymeric and Lipid based nanocarriers for oral GLP-1 analogue delivery

OP-10 – 17:30-17:45 **Blaž Grilc**, Maja Bjelošević, Mirjana Gašperlin
Lactoferrin micro-encapsulation in Na-alginate hydrogel beads

OP-11 – 17:45-18:00 **Jelena Đoković,** Snežana Savić
Curcumin loaded PEGylated nanoemulsions: development and physicochemical characterization towards in vivo pharmacokinetic experiments

OP-12 – 18:00-18:15 **Areen Alshweiat**, IIdikó Csóka, Rita Ambrus
Nanosystems for improved physicochemical properties of poorly water soluble loratadine

OP-13 – 18:15-18:30 **Zsófia Németh**, Dorina Dobó, Edina Pallagi, Ildikó Csóka
Quality by Design-based approach to liposomal development

OP-14 – 18:30-18:45 **Aleksandra Gavaric**, Senka Vidovic
Optimization of bioactive compounds of horehound extracts obtained using ultrasound and microwave assisted extraction: anti-hyperglycaemic activity

19:30- Networking event

Friday, 24th January

9:00-10:45 Section 3. – Chair: Prof. Dr. Senka Vidovic, Dr. Zoltán Aigner

OP-15 – 9:00-9:15 **Krisztina Ludasi**, Géza Regdon jr.
Development of QR coded tablets for anti-counterfeiting of drugs by laser technology

OP-16 – 9:15-9:30 **Eszter L. Kiss**, Erzsébet Csányi, Mária Budai-Szűcs
Nanostructured lipid carriers for ophthalmic use

OP-17 – 9:30-9:45 **Ana Ćirić,** Ljiljana Đekić
Characterization of chitosan/xanthan polyelectrolyte complex carriers: Influence of drug encapsulation procedure on in vitro release kinetics

OP-18 – 9:45-10:00 **Yasmin Ranjous**, Géza Regdon jr., Tamás Sovány
The prominence of titanate nanotubes' functionalization on their physicochemical properties and biological applications as drug delivery system

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

January 23-24th 2020. Szeged, Hungary

OP-19 – 10:00-10:15 **Kinga Ilyés,** Ioan Tomuță
3D-printing by fused deposition modelling in pharmaceutics

OP-20 – 10:15-10:30 **Edit Benke**, Piroska Szabó-Révész, Rita Ambrus
Characterization of dry powder inhalation systems using an organic solvent to reach special micrometric properties

OP-21 – 10:30-10:45 **Maja Bjelošević**, Mirjam Gosenca Matjaž, Mirjana Gašperlin, Pegi Ahlin Grabnar
The effect of bovine serum albumin concentration on lyophilized formulation characteristics

10:45-11:00 Break

11:00-12:30 Section 4. – Chair: Prof. Dr. Mirjana Gašperlin, Dr. Tamás Sovány

OP-22 – 11:00-11:15 **Hussein Akel**, Ildikó Csóka
Lipid based nanosystem designed for nose to brain delivery of Alzheimer Disease Drug

OP-23 – 11:15-11:30 **Balázs Attila Kondoros**, Zoltán Aigner
Physicochemical characterization and dissolution studies of terbinafine hydrochloride–cyclodextrin complexes prepared by solvent-free co grinding

OP-24 – 11:30-11:45 **Amina Tucak**, Merima Sirbubalo, Andreas Zimmer, Edina Vranić
Cationic nanostructured lipid carriers (cNLCs) as drug delivery systems for miRNA: investigations of formulation and process parameters

OP-25 – 11:45-12:00 **Andrea-Gabriela Crișan,** Ioan Tomuță
Fused Deposition Modeling Three-Dimensional Printing (FDM-3DP) of Channelled Tablets with Ketoprofen: Design, Development and Pharmaceutical Evaluation

OP-26 – 12:00-12:15 **Ivana Vasiljević,** Jelena Parojčić
Powder Compressibility Assessment: Manufacturability Classification System vs. SeDeM Expert System

OP-27 – 12:15-12:30 **Rita Máthé**, Tibor Casian, Ioan Tomuţă
Multivariate modelling for investigating the impact of raw materials and process variability on high drug load immediate release tablets obtained through wet granulation

12:30-13:45 Lunch break

13:45-15:30 Section 5. – Chair: Dr. Rita Ambrus, Dr. Edina Pallagi

OP-28 – 13:45-14:00 **Ernő Máté Benkő**, Tamás Sovány, Ildikó Csóka
API – excipient interactions in solid matrix systems

OP-29 – 14:00-14:15 **Stella Zsikó**, Erzsébet Csányi, Szilvia Berkó
Study of Skin Penetration Testing Methods

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

January 23-24th 2020. Szeged, Hungary

OP-30 – 14:15-14:30 **Jelena Mitrović,** Miroslav Savić, Snežana Savić
Nano-crystalline suspensions of novel pyrazoloquinolinones ligand (DK-I 56-1): physicochemical and in vivo pharmacokinetic and behavioural characterization

OP-31 – 14:30-14:45 **Patience Wobuoma**, Ildikó Csóka
Formulation and investigations of lysozyme nanoparticle

OP-32 – 14:45-15:00 **Ines Nikolić,** Snežana Savić
Low-energy nanoemulsions for curcumin delivery: investigation of the interfacial phenomena in the colloidal system and peculiarities important for biological performances

OP-33 – 15:00-15:15 **Nikolett Kis**, Szilvia Berkó, Erzsébet Csányi
Investigation of semi-solid in situ film-forming systems with QbD approach

OP-34 – 15:15-15:30 **Yousif Ibrahim**, Katalin Kristó, Géza Regdon jr., Tamás Sovány
Effect of Processing Conditions and Material Attributes on the Design Space of Lysozyme Pellets Prepared by Extrusion/Spheronization

15:30-15:45 Break

15:45-17:30 <u>Section 6.</u> – Chair: Dr. Eva Šnejdrová, Dr. Szilvia Berkó

OP-35 – 15:45-16:00 **Tamás Kiss**, Rita Ambrus
Treatment of the off-periods of Parkinson's disease with levodopa and its derivative

OP-36 – 16:00-16:15 **Luca Éva Uhljar**, Rita Ambrus
Investigation of bottom-up prepared nanostructures

OP-37 – 16:15-16:30 **Reihaneh Manteghi**, Gerda Szakonyi, Ildikó Csóka
PEGylation and formulation strategies of antimicrobial peptides and proteins development

OP-38 – 16:30-16:45 **Mahwash Mukhtar**, Rita Ambrus
Development of Inhalable Chitosan nano system conjugated with Hyaluronic acid for treatment of Tuberculosis

OP-39 – 16:45-17:00 **Fakhara Sabir**, Ildikó Csóka
Significance of QbD in design and development of coated liposomes for nose to brain delivery

OP-40 – 17:00-17:15 **Krisztián Pamlényi**, Katalin Kristó, Géza Regdon jr.
Development and characterization of sodium alginate polymer film as a buccal mucoadhesive drug delivery system

OP-41 – 17:15-17:30 **Zorica Drinić**, Senka Vidović
Influence of process parameters on supercritical carbon dioxide extraction of cannabidiol from Cannabis sativa L. aerial parts

17:30-17:45 Closing remarks

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

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Abstracts

OP-1

DOI: 10.14232/syrptbrs.2020.op1

In vitro and *ex vivo* investigation of steroid containing ocular drug delivery systems

Tivadar Bíró, Zoltán Aigner

Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged, Szeged, Hungary

The poor bioavailability in ocular drug delivery is well known, which is mostly caused by the special defensive mechanisms and complex anatomical structure of human eye. Possibilities are known for inducing enhanced therapeutic efficacy - due to increasing the solubility of drug and the residence time on the eye surface. Formulation specialists need to ensure not only the optimal drug permeation but also the required microbiological stability. The widely applied benzalkonium-chloride is toxic on the corneal epithelial cells, therefore use of alternative, nontoxic preservative agents is needed [1].

Cyclodextrin containing, mucoadhesive ocular drug delivery systems were optimized by our research group. Results of mucoadhesion, surface tension, viscosity, *in vitro* drug diffusion and antimicrobial effectiveness test were previously published [2]. Afterwards, *in vitro* toxicity and permeability were studied on human corneal epithelial cell line, and *ex vivo* drug permeability was tested using porcine corneal model. As the results show, toxicity and permeability are more suitable, than benzalkonium-chloride containing compositions or suspension forms. In summary, the prepared formulations could be innovative approaches for steroid containing eye drops with increased bioavailability.

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2. Bíró T. et al. Drug Des. Dev. Ther. 12, 2529-2537 (2018)

Acknowledgements

This work was supported by the UNKP-19-3-SZTE-26 New National Excellence Program of the Ministry for Innovation and Technology

Supervisor: Zoltán Aigner

OP-2

DOI: 10.14232/syrptbrs.2020.op2

Spray vs freeze-dried solid lipid microparticles: Challenges in development

Jelisaveta Ignjatović, Sandra Cvijić, Jelena Đuriš

Department of Pharmaceutical Technology and Cosmetology, University of Belgrade-Faculty of Pharmacy, Belgrade, Serbia

Lipid particles appeared as an alternative carrier to traditional polymeric microparticles and nanoparticles. Although lipid microparticles (LMs) can be delivered by common routes (oral, topical and parenteral), LMs can take advantage over other carriers due to their size, and be the most appropriate for specific administration routes (e.g. pulmonary) [1]. For the purpose of this study, QbD approach was applied in formulation and production of solid lipid microparticles (SLMs) using glyceryl dibehenate or stearyl alcohol. SLMs were prepared by melt emulsification method in conjunction with freeze or spray-drying, in order to obtain water-free particles. Ishikawa diagram was constructed to identify the parameters that could affect the quality of SLMs. SLMs size, morphology, density, drug content, dissolution rates and *in vitro* aerosol performance were evaluated for selected samples. Results have indicated that spray-dried SLMs had smaller particle size and higher drug content than freeze-dried SLMs. In addition, spray-dried samples were porous particles with lower true density (approximately 1 g/cm^3). Consequently, aerodynamic performance of several spray-dried samples was satisfactory since they exhibited fine particle fraction (FPF) > 20%, which is a respectable percentage for this type of formulations, where FPF values of 20-30% were usually observed. Dissolution studies showed that slower drug release can be achieved when glyceryl dibehenate was used regardless of the drying method.
It can be concluded that spray-dried SLMs can be potential formulations for pulmonary drug delivery whereas freeze-dried SLMs are more suitable for other administration routes.

References

1. Scalia S, Young PM, Traini D. Expert Opin. Drug Deliv. 12(4), 583-599 (2015)

Supervisor(s): Dr Jelena Đuriš, Dr Sandra Cvijić

OP-3

DOI: 10.14232/syrptbrs.2020.op3

Formulation of nasal drug delivery systems to induce systemic and central nervous systemic effect

Péter Gieszinger, Rita Ambrus, Piroska Szabó-Révész

Institute of Pharmaceutical Technology and Regulatory Affairs, Interdisciplinary Excellence Centre, University of Szeged, Szeged, Hungary

In the last decades the nose has become one of the most researched among the alternative drug administration routes. The reason of the considerable attention is, that due to its unique anatomical and physiological properties, local, systemic and direct Central Nerve System (CNS) effects can be available. In the case of those 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 [1]. Particle size decreasing into the nano range is an up-to-date and common way to modify the properties of drugs that can affect its bioavailability in a positive way [2]. The aim of this research is to formulate and develop nasal 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]. Also, a LAM containing nanocapsule (NC) formulation has been produced and investigated *in vitro* and *in vivo*.

ACKNOWLEDGEMENT

Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT is acknowledged.

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2. Zhi H. L. et al. Asian. J. Pharm. 10, 255-274 (2015)
3. Serralheiro A. et al. Int. J. Pharm. 490, 39–46 (2015)
4. Gieszinger P. et al. Drug Dev. Ind. Pharm. 44, 1622-1630 (2018)

Supervisor(s): Rita Ambrus, Piroska Szabó-Révész

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

January 23-24th 2020. Szeged, Hungary

OP-4

DOI: 10.14232/syrptbrs.2020.op4

Formulation of medicated nanoparticles based on branched PLGA

Juraj Martiška, Eva Šnejdrová, Milan Dittrich

Department of Pharmaceutical Technology, Faculty of Pharmacy in Hradec Kralove, Charles University, Hradec Kralove, Czech Republic

Poly(lactic-*co*-glycolic acid) (PLGA) is currently the most widely used biomaterial for encapsulation and prolonged delivery of therapeutic drugs, proteins and antigens [1]. We introduce originally synthesized branched PLGA derivatives with lower molar mass, and star or comb architecture as promising biodegradable carriers for prolonged or targeted drug release systems [2]. These polyesters were used as starting materials for nanoparticles formulation by nanoprecipitation, and double-emulsion method. We successfully incorporated various molecules such as Terbinafine, Rifampicin, and Small interfering RNA (siRNA). Multiple parameters as particles size, polydispersity, zeta potential, encapsulation efficiency, and loading capacity were monitored. Morphology of the nanoparticles was studied by scanning electron microscope (SEM). The use of the polymers with tailored properties resulted in formulation of the nanoparticles with desired particle size, mucoadhesive properties, and prolonged drug release profile which we attribute to the gradual swelling and degradation of the polyester in an aqueous medium [3]. The hydrophobicity and the polyester concentration revealed the main impact on the nanoparticles size ranging from 100 to 600nm [4]. Examined polyesters are perspective, original, and suitable for further observation.

References

1. Han F. Y. et al. Front. Pharmacol. 7:185, (2016)
2. Snejdrova E. et al. Acta Pharm. 70, 63-75 (2020)
3. Dittrich M. et al. J. Pharm. Sci. 103, 3560-3566 (2014)
4. Martiska J. et al. Pharm. Dev. Technol. 24(10), 1308-1316 (2019)

Supervisor(s): Assoc. Prof. RNDr. Milan Dittrich, CSc; PharmDr. Eva Snejdrova, PhD.

Acknowledgement

This work was supported by the Funding Agency of Charles University under Grant SVV 260401.

OP-5

DOI: 10.14232/syrptbrs.2020.op5

PLA-based nanofibrous systems for the treatment of periodontal disease

Attila Léber, Erzsébet Csányi, Mária Budai-Szűcs

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The plaque-induced forms of periodontal diseases are the most prevalent chronic inflammatory conditions seen in humans worldwide. Not only does it cause tooth loss, but it is also independently associated with systemic chronic inflammatory diseases [1—2].

The aim of this study was to develop and characterize a PLA-based nanofibrous drug delivery system containing metronidazole for local periodontitis treatment.

Delivery systems were characterized in the form of native fiber mats and compressed disks. Scanning electron microscopy, X-ray diffraction analysis, and different measurements were carried out regarding wettability, *in vitro* drug release, and antimicrobial effectiveness.

Results of the X-ray diffraction analysis suggest that PLA has a semi-crystalline structure, while metronidazole is in a crystalline form among the fibers. SEM pictures indicate that fibers are not damaged during compression. Wettability measurements show that the penetration of an aqueous medium is much easier in the case of fiber disks than in fiber mats. In vitro drug diffusion measurements revealed that – in accordance with the wettability results – the fiber mats and disks show different drug release profiles: disks provide rapid (24 h) dissolution of metronidazole, while mats exhibit sustained (96 h) drug release. Results of the microbiological study suggest that disks could inhibit the growth of disease-inducing anaerobic bacteria for 2—3 days.

In conclusion, the produced delivery systems could supplement or be an alternative to subgingival mechanical debridement and contribute to an effective periodontitis treatment.

References

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Acknowledgements

This work was supported by the ÚNKP-19-3-SZTE-175 New National Excellence Program of the Ministry for Innovation and Technology.

Supervisors: Erzsébet Csányi, Mária Budai-Szűcs

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

January 23-24th 2020. Szeged, Hungary

OP-6

DOI: 10.14232/syrptbrs.2020.op6

Influence of experimental model, active substance and polymer type on mucoadhesive properties of buccal tablets

Ivana Kurcubic, Jelena Đuriš

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Mucoadhesiveness is influenced by the presence of different excipients and active substances that increase or decrease the interaction strength between polymer chains and mucosal surface. Mucoadhesive properties of buccal tablets were determined by measurement of the work of adhesion required to separate the test formulation from the mucosa-mimetic material: mucin disc or mucin dispersion (TA.XT plus texture analyzer equipped with thermostated mucoadhesive rig) [1]. The aim of the present study was to compare the usefulness of mucin disc and 10% mucin dispersion and to determine the influence of the mucoadhesive polymers (PEO, HPMC) as well as propranolol hydrochloride (PR) on the mucoadhesive properties of buccal tablets. Both mucosa-mimetic models enable determination of mucoadhesiveness, however, the lowest values of work of adhesion were obtained using mucin dispersion. By analyzing of placebo tablets using mucin disc revealed a statistically significant difference only between the $F1_P$ and $F6_P$ formulations. These are tablets that contain the highest PEO polymer content and the lowest HPMC polymer content, respectively. Incorporation of PR into PEO based tablets led to a slight decrease in mucoadhesiveness, whereas in the case of HPMC based tablets an increase in mucoadhesiveness was observed. The highest W_{ad} was achieved with high concentration PEO ($F1_P$) tablets.

Mucin disc and mucin dispersion serve as suitable surrogates, however more measurements are necessary to obtain reliable results. Addition of PR led to increase in mucoadhesiveness in certain formulation, while the type of polymer didn't affect the mucoadhesive properties.

References

1. Andrews GP. Biomacromolecules. 10(9), 2427–2435 (2009)

Supervisor(s): Professor Jelena Đuriš

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

January 23-24th 2020. Szeged, Hungary

OP-7

DOI: 10.14232/syrptbrs.2020.op7

QbD development of a liposomal co-formulation with Doxorubicin and Simvastatin for an enhanced antiproliferative effect on T47D-KBluc cell line

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[2] Department of Toxicology, Faculty of Pharmacy, University of Medicine and Pharmacy "Iuliu Hațieganu", Cluj-Napoca, Romania

The aim of the research was to develop a liposomal co-formulation with doxorubicin (DOX) and simvastatin (SIM). DOX is known for its high toxicity and thus, its association with a compound that also presents antiproliferative properties, like SIM, was explored in order to obtain a synergic/ additive effect.

The Quality by Design (QbD) concept was applied for liposomes development to get a better understanding of how the selected formulation factors and process parameters (PPs) can influence the quality attributes (QAs) of the liposomes. In accordance with this, risk assessment was performed and hence, three formulation factors and two PPs were selected to be studied in a screening experimental design. The results showed that all three formulation factors, namely phospholipids, DOX and SIM concentration, had a great influence on the liposomes QAs like encapsulated drug concentration and encapsulation efficiency (EE%). As regards the PPs, only the pH of the ammonium sulphate solution was pointed out to have a slight influence on DOX EE%.

Considering the results from the screening study, the optimization process was performed by means of a design of experiments with the aim of obtaining a design space and an optimal formulation which fulfils all our requirements.

The antiproliferative effects of the combined administration of SIM and DOX was studied on T47D-KBluc breast cancer cell line, indicating a strong inhibitory activity.

In conclusion, the co-administration of DOX and SIM in a liposomal formulation is a promising solution to inhibit the proliferation of T47D-KBluc breast cancer cells.

Acknowledgements: University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Romania; internal grant no: 1529/7/18.01.2019

Supervisor(s): Prof. Dr. Ioan Tomuță; Assoc. Prof. Dr. Alina Porfire

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

January 23-24th 2020. Szeged, Hungary

OP-8

DOI: 10.14232/syrptbrs.2020.op8

Stearylamine-based nanoemulsion: preparation, characterization and physical stability investigation

Merima Sirbubalo[1], Amina Tucak[1], Edina Vranić[1], Andreas Zimmer[2]

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Oil-in-water cationic nanoemulsions (CNE) are fine dispersions consisting of an oil core (from natural or synthetic origin) stabilized by a single cationic lipid or a mixture with phospholipids, non-ionic surfactants, and/or PEG-lipids. CNEs are considered to be suitable and potential delivery system for nucleic acids in gene therapy field due to their positively charged surface which complex with negatively charged gene material through electrostatic interactions [1]. The aim of the present study was to evaluate the effect of cationic lipid-sterylamine (SA) on mean droplet size, zeta potential and pH of the CNEs. Formulations containing various concentrations of SA were prepared on high-pressure homogenizer. The mean droplet size and zeta potential of the emulsions were determined by photon correlation spectroscopy and electrophoretic light scattering, respectively (Malvern NanoZs Zetasizer). The mean droplet size of emulsions varied from 126 to 129 nm while the polydispersity index varied from 0,068 to 0,137. As expected, zeta-potential increased from +43,7 mV to +53,7 mV with the SA concentration increase from 0,25 to 0,75 % (*w/w*). During the 60-day storage period at 25 °C, the droplets stayed in the nanometer range with only a minor size increase (~10 nm), no significant changes in droplet size distribution nor zeta potential or any difference in their visual appearance (no creaming or phase separation) proving therefore a satisfactory formulation stability.

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Supervisor(s): Prof. dr. Edina Vranić and Univ.-Prof.dr. Andreas Zimmer

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

January 23-24th 2020. Szeged, Hungary

OP-9

DOI: 10.14232/syrptbrs.2020.op9

Potential of polymeric and Lipid based nanocarriers for oral GLP-1 analogue delivery

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Glucagon-like peptide-1 analogues, liraglutide (Lira) and exenatide (Exn), are currently limited to subcutaneous injections in clinical protocols [1]. Due to several drawbacks accompanied with this invasive route, the development of oral delivery system is likely the most attractive choice. Among the various strategies having been developed to conquer the barriers limiting oral peptide delivery [2], [3], the encapsulation of GLP-1 analogues into nanosystems seem to be very promising strategy. Herein, the aim is to discuss the potential of designing polymeric nanosystem and self-emulsifying drug delivery system (SEDDS) for oral delivery of Lira and Exn. Due to the complexity and nanotoxicological concerns of nanopharmaceuticals in addition to the risks entailed with peptides formulation development, it is critical to focus on quality by design (QbD) application when developing nanocarriers encapsulating peptide aiming to develop a thorough understanding of the target product and process design [4].

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Supervisor: Ildikó Csóka

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

January 23-24th 2020. Szeged, Hungary

OP-10

DOI: 10.14232/syrptbrs.2020.op10

Lactoferrin micro-encapsulation in Na-alginate hydrogel beads

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Whey, co-product of milk processing was considered for years as a waste material and thus represented environmental burden. However, due to its protein rich composition, different scientific areas are oriented to the exploitation of whey potential. Lactoferrin (Lf) is an iron-binding whey protein, which has antimicrobial, immunomodulatory, and antioxidant activities, thus expressing several beneficial effects on human health [1].

The objective of the study was to develop and optimize composition of microcapsules with alginate and Lf, along with selection of appropriate microencapsulation parameters, drying process and conditions.

Formulations with different alginate/ Lf ratios in water were prepared and subjected to microencapsulation by utilizing encapsulator Inotech IE-50 R in cross linking solution containing Ca^{2+} ions. Size distribution of dried microcapsules was evaluated through the image analysis and Lf content was determined by reverse phase HPLC.

Obtained results revealed that by increasing Lf/ alginate ratio in initial dispersion (i.e. from 1:1 to 2:1) size of microcapsules also increased, however by further increase of Lf/ alginate ratio to 4:1 no additional changes were observed. Moreover, due to the leakage of Lf from the core of the microcapsules, only a minor differences in Lf content were demonstrated.

Our results suggest that by incorporation Lf in alginate dispersion microcapsules can be prepared and formulated in final dosage form for oral administration. However, by appropriate formulation composition and inclusion of additional excipients leaking of Lf has to be further investigated.

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Supervisor(s): Mirjana Gašperlin

OP-11

DOI: 10.14232/syrptbrs.2020.op11

Curcumin loaded PEGylated nanoemulsions: development and physicochemical characterization towards in vivo pharmacokinetic experiments

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PEGylated nanoemulsions (NEs) can increase target site concentration of the incorporated active by increasing circulation time of the oil droplets [1]. Using experimental design approach best preparation conditions were chosen for further research. Curcumin was used as a model drug and incorporated into formulations selected by experimental design. The aim of this study was to follow the stability of PEGylated and the non-PEGylated NEs and to assess the impact of PEGylated phospholipids' (PEG-PLs) addition on nanoemulsions' long term stability. Additionally, the impact of PEG-PLs on drug release was assessed through *in vitro* drug release studies in order to choose the best candidates for *in vivo* pharmacokinetic study.

NEs were prepared by high pressure homogenization [2]. Nanoemulsions' stability was followed for 12 months by measuring mean droplet size (Z-ave), polydispersity index (PDI) and zeta potential (ZP). Drug release was studied by reverse dialysis bag method.

Initial Z-ave of all NEs (103–106 nm), PDI (< 0.2) and ZP around –40 mV, suggested they are adequate for parenteral application. After 12 months these parameters did not significantly change. During in vitro release study the biggest release of curcumin was from the formulation containing 0.3% of PEG5000DPPE (43.38%) vs the lowest with 0.1 % of PEG2000DSPE (25.88%).

This study showed the usefulness of D-optimal factorial design in NEs development. Formulations containing 0.1 % of PEG2000DSPE/PEG5000DPPE were chosen for further step - a pharmacokinetic study.

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Supervisor: Snežana Savić

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

January 23-24th 2020. Szeged, Hungary

OP-12

DOI: 10.14232/syrptbrs.2020.op12

Nanosystems for improved physicochemical properties of poorly water-soluble loratadine

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Recently, nanosystems have been developed to improve drug properties and facilitate delivery. In practice, nanosystems contain particles within a particle size of less than 1000 nm. Loratadine (LOR) is a H1 antihistamine drug commonly prescribed for the treatment of allergic conditions. LOR has poor aqueous and pH-dependent solubility. Consequently, the oral administration is associated with variable and poor bioavailability.

This study investigated the preparation of LOR nanosystems using top-down technologies, particularly precipitation and electrospraying. The critical process and material parameters have been identified and optimized in light of the required attributes.

The two different approaches had different morphologies and physicochemical properties. Therefore, different solubility and dissolution rates. On the other hand, LOR showed an amorphous state in both systems [1].

The nanosystems displayed a particle size of the range of 168-254 nm of LOR nanosuspensions and 372 nm diameter for the nanofibers. In the first 10 min, the nanosystems showed dissolution rates of 30–42% and 66% for the nanosuspensions and nanofibers, respectively [2–3].

The reduction of the particle size is associated with improved dissolution rate, thus bioavailability. Moreover, this improvement could enable the design of new alternative LOR formulations, including buccal, transdermal, and topical dosage forms.

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Supervisors: Rita Ambrus, IIdikó Csóka.

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

January 23-24th 2020. Szeged, Hungary

OP-13

DOI: 10.14232/syrptbrs.2020.op13

Quality by Design-based approach to liposomal development

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Quality by Design (QbD) is a new perspective to replace the traditional, "in-process study"-based quality control procedures of the Quality by Testing (QbT) method, which concept has been started to use in the pharmaceutical developments since the beginning of the 2000s.

The objective of our research project was to conduct a QbD-based development process to prepare liposomal formulations and thus investigate the effects of various production parameters (filtration, pressure, and temperature) and different compositions (phospholipid-cholesterol ratios, hydration media, and cryoprotectants).

The liposomal formulations were prepared by the thin-film hydration method [1]. The temperature and the pressure during the production were changed in addition to the filtration, as well as the ratio of the wall-forming agents. The products were investigated via dynamic light scattering technique to determine the vesicle size and the size distribution, and the zeta potential values were checked. The thermostability of the samples was analysed via differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) measurements. N_2 adsorption and desorption isotherms were measured to define the characteristics of the vesicular surface and the structure of the vesicles was verified via transmission electron microscopy (TEM).

The size of the prepared vesicles was under 200 nm, and the zeta potential values were slightly negative, except the API-containing formulations.

The results showed that the quality of the development process can be improved via the application of the QbD-based approach in the case of the liposomal formulations.

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Supervisors: Edina Pallagi, Ildikó Csóka

Acknowledgements

This work was supported by the Gedeon Richter's Talentum Foundation and the Gedeon Richter Plc. Centennial Foundation, the Pharmacia Foundation the Ministry of Human Capacities, Hungary grant 20391 3/2018/FEKUSTRAT (Interdisciplinary Excellence Centre) and the construction EFOP 3.6.3-VEKOP-16-2017-00009. The project was sponsored by the European Union, co-financed by the European Social Fund and supported by the ÚNKP-19-3-SZTE-61 New National Excellence Program of the Ministry for Innovation and Technology.

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

January 23-24th 2020. Szeged, Hungary

OP-14

DOI: 10.14232/syrptbrs.2020.op14

Optimization of bioactive compounds of horehound extracts obtained using ultrasound and microwave assisted extraction: anti-hyperglycaemic activity

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White horehound (*Marrubium vulgare* L.) is a grey-leaved perennial herb, belonging to Lamiaceae family, distributed in Eurasia and northern Africa zones [1]. According to the recent literature, horehound shows several *in vivo* and *in vitro* activities including antihypertensive, antioxidant, antiinflammatory, antidiabetic, effects on respiratory system, digestive stimulant, antiasthmatic, hypolipidemic, antibacterial and antifungal effects [2,3,4,5,6,7]. Having a scarce information about ultrasound assisted extraction (UAE) of horehound and several articles focusing on intensification of marrubiin content by microwave assisted extraction (MAE), the idea to compare these modern extraction techniques imposed. UAE and MAE were confronted in reference to extraction yield, polyphenols content, antioxidant potential and antidiabetic activity. Response surface methodology was used for optimization of process parameters in UAE and MAE. The optimal UAE parameters for maximized polyphenols and antioxidant activity were temperature of 73.6 °C, extraction time of 40 min and ultrasound power of 30.3 W/L, while in case of MAE the optimal parameters were 63.8% ethanol, extraction time of 15 min and microwave power of 422 W. The optimal UAE and MAE extracts were subjected to α-amylase and α-glucosidase inhibitory assays to determine their anti-hyperglycaemic potential.

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Supervisor: dr Senka Vidovic

OP-15

DOI: 10.14232/syrptbrs.2020.op15

Development of QR coded tablets for anti-counterfeiting of drugs by laser technology

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Counterfeit drugs pose a growing threat to our health as they can lead to hazardous treatment or even cause death. According to the WHO reports from 2017, the failure rate of these medical products is approximately 10.5% [1]. Drugs purchased on the Internet could be fake in 50% [2].

According to Directive 2011/62/EU to protect the pharmaceutical supply chain from substandard and falsified medicines, individual identification should be put on the packaging of prescription medicines. We are working on developing a unique traceable QR code placed on the surface of the tablet [3]. With this technology, even patients would be able to authenticate these drugs by a mobile phone with suitable application.

Coated tablets were marked by different types of lasers (YAG laser, excimer laser, semiconductor laser). Analytical quality control was carried out on the tablets to check if there occurred any change during the laser coding, by SEM, Raman, Thermogravimetry and Mass spectrometry.

It was found that some lasers with particular parameters are suitable for marking a unique code on tablets against counterfeiters, and others are not. Personalized medicines could also be labelled in this way.

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Supervisor: Géza Regdon jr.

OP-16

DOI: 10.14232/syrptbrs.2020.op16

Nanostructured lipid carriers for ophthalmic use

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The development of ophthalmic formulations is a major challenge. The most commonly used ophthalmic formulations are eye drops which have low bioavailability due to the complex structure and the elimination mechanisms of the eye [1].

Nanostructured lipid carrier (NLC) is the term used for the second-generation solid lipid nanoparticles that contain a lipid matrix of mixed solid and liquid lipids. These systems are ideal to incorporate low water-soluble active substances such as corticosteroids [2].

The aim of this work was to create a dexamethasone (DXM) loaded NLC formulation to increase the bioavailability of DXM, which is a lipophilic drug with poor solubility in water. As a preformulation study, lipid screening (visual observation, XRD, DSC measurements and investigation of blank NLCs) were applied to choose the most suitable excipients for the formulation of the system. A 2^3 factorial design was used to investigate the effects of the excipients on zeta potential, mean particle size, PDI and entrapment efficacy. The independent factors were lipid, DXM and surfactant concentration. Based on the one-month stability test, a lower surfactant and lipid concentration could be beneficial. The ophthalmic toxicity was investigated on human cornea cells and the results show that the measured NLC formulations have good ophthalmic tolerability. The *in vitro* drug release study suggests that the NLC formulations increase the diffused amount of DXM in the acceptor phase, while the penetration study on porcine cornea with Raman mapping predicted a higher amount of nanocarriers in the stroma layer.

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Supervisors: Mária Budai-Szűcs, Erzsébet Csányi

OP-17

DOI: 10.14232/syrptbrs.2020.op17

Characterization of chitosan/xanthan polyelectrolyte complex carriers: Influence of drug encapsulation procedure on *in vitro* release kinetics

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Chitosan/xanthan polyelectrolyte complexes (PECs) are considered promising oral drug delivery carriers due to nontoxicity, biodegradability and can be investigated as potential carriers for extended drug release [1,2]. Ibuprofen has short half-life ($t_{1/2}$~2 h) and requires frequent administration of immediate release dosage forms [3]. The aim of this study was to investigate the influence of the ibuprofen encapsulation procedure on its *in vitro* release kinetics. Dried PECs, prepared with chitosan solutions adjusted to pH 4.6 using acetic acid, and ibuprofen dispersed in the xanthan solution before (4.6B) or added after (4.6A) the complexation of polymer aqueous solutions, comprising 100 mg of ibuprofen, were filled into size 0 capsules. *In vitro* release profiles in the paddle apparatus (50 rpm) (Erweka DT70, Germany) were obtained using 900 ml of phosphate buffer pH 7.2 at 37 ± 1 °C. Both samples showed extended ibuprofen release during 12 h. From 4.6B 100% of ibuprofen was released after 12 h. From 4.6A 66.41 ± 2.14% of substance was released after the same time. Ibuprofen release from the samples followed the *Korsmeyer-Peppas* kinetics and the release mechanism was a combination of swelling, erosion and diffusion ($0.5<n<1$). PEC 4.6B showed better control of ibuprofen release and its preparation conditions are considered optimal for controlled extended drug release.

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Supervisor(s): Dr. Ljiljana Đekić, Associate Professor

OP-18

DOI: 10.14232/syrptbrs.2020.op18

The prominence of titanate nanotubes' functionalization on their physicochemical properties and biological applications as drug delivery system

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Ceramic materials such as titania are hydrophilic by nature due to the existence of hydroxyl groups, which limits their applications. Therefore, the hydrophobization process is needed in order to improve their permeability and other physicochemical properties besides decreasing their toxicity [1].

In the previous stage of the study composites of TNT with atenolol (ATN) and hydrochlorothiazide (HCT) were formed using various solvents [2]. The physicochemical properties of the samples were investigated by using TEM (FEI, OR, USA) and SEM (Hitachi, Japan) imaging to analyze the texture, an optical contact angle tester (DataPhysics, Germany) to determine the surface free energy, a FT-IR spectrometer (Thermo Fisher Scientific Ltd., MA, USA), and a DSC/TG apparatus (Mettler-Toledo Ltd, Hungary) to detect the interaction between drugs and TNTs. According to the results, the appropriate choice of the solvent leads to a better quality of the formed composite, which results in improved dissolution properties. However, the composite was found to be unable to be absorbed as drug delivery system. Therefore, TNTs were functionalized by using trichlorooctylsilane, trichloroocatdecylsilane and Mg stearate in order to improve their permeability and decrease toxicity.

The characterization of functionalized TNTs was assessed by using TGA, OCA, CHNS elemental analyser and FT-IR. Toxicity was studied with MTT assays while the result of the permeability study was evaluated with an X-ray fluorescent analyser.

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Supervisors: Géza Regdon jr., Tamás Sovány

OP-19

DOI: 10.14232/syrptbrs.2020.op19

3D-printing by fused deposition modelling in pharmaceutics

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Fused deposition modelling (FDM), constitutes a versatile and cost-effective representative of the 3D-printing (3DP) techniques. With roots in engineering, it was first considered for pharmaceutical purposes based on its potential of personalization.
Compared to the conventional powder compaction methodologies, in this case the tablet is constructed from melted and extruded subsequent layers. As, for the drug, it is incorporated within a filament, which for appropriate mixing and loading purposes, nowadays is manufactured via preliminary hot melt extrusion (HME).
The integration of 3DP-FDM in pharmaceutics is promising. The technology is capable of producing a wide palette of designs that normally are hard to produce, like channelled, layered, compartmented tablets, associating one or several APIs and release profiles. It can also bring quality improvements compared to conventional dosage forms. Case study proved that high quality floating tablets can be obtained via HME+FDM [1].
Still, the adaptation of pharmaceutical polymeric blends to FDM can be difficult as the appropriate rheological and mechanical equilibrium for the filaments is hard to obtain [2].

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Acknowledgements

University of Medicine and Pharmacy "Iuliu Hațieganu" doctoral research grant 1531/3/18.01.2019, Collegium Talentum 2019 Programme of Hungary.

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OP-20

DOI: 10.14232/syrptbrs.2020.op20

Characterization of dry powder inhalation systems using an organic solvent to reach special micrometric properties

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Pulmonary drug delivery represents a new alternative treatment way for both local and systemic diseases (where, in addition to its beneficial properties, one-tenth of the active ingredient is sufficient to achieve the required effect by oral administration [1]). To accomplish this, the international literature distinguishes between nebulizers, pressurized metered-dose inhalers, and dry powder inhalers (DPIs). The development of the latter can be considered a "hot topic" these days, due to a large number of formulation options available. A number of solid excipients are being tested for their effect on aerosolization [2], but not a lot of data are currently available on the aerosolization effect of organic solvents (OSs) used in DPI sample preparation [3]. Thus, the purpose of the present work was to investigate the effects of a given OS in different concentrations on powder properties and *in vitro* lung model results of DPI formulations, and to develop the microcomposites for pharmaceutical form prepared in the ideal percentage of OS using different DPI capsule types in stability test. The study showed that the percentage of the OS of our choice during spray drying production influences the physical properties of the samples and thus the aerosolization. As a result of the formulations development for pharmaceutical form made in the optimal percentage of the applied OS, remarkable differences in the stability investigations were found through various DPI capsule properties.

Acknowledgment

This project was supported by the UNKP-19-3-SZTE New National Excellence Program of the Ministry for Innovation and Technology and by the EFOP-3.6.3-VEKOP-16-2017-00009 project.

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Supervisor: Rita Ambrus

OP-21

DOI: 10.14232/syrptbrs.2020.op21

The effect of bovine serum albumin concentration on lyophilized formulation characteristics

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Biopharmaceuticals represent one of the crucial areas in the pharmacy and are widely used to treat several diseases. Protein molecules are typically unstable in aqueous media, thus lyophilisation is the method of choice to transform such formulations into solid state. Initially biopharmaceuticals were intended for intravenous administration, whereas current trends are oriented in development of protein formulations for subcutaneous administration, which is associated with many challenges [1].

The main aim was to evaluate the effect of bovine serum albumin (BSA) concentration on formulation viscosity, further on related to critical quality attributes of lyophilized formulations, such as reconstitution time and visual appearance.

Formulations with five different BSA concentrations (5, 20, 50, 70 and 100 mg/mL) in phosphate buffer and sucrose or sucrose/mannitol as excipients were subjected to lyophilisation. Lyophilised products were evaluated for visual appearance, reconstitution time and particle size by dynamic light scattering. In addition, viscosity and thermal characteristics of pre-lyophilized solutions were determined.

Obtained results revealed that by increasing BSA concentration the reconstitution time was prolonged, while cake appearance was improved. Independent of formulation composition, the particle diameter was below 9 nm indicating absence of aggregates. Furthermore, an increase of viscosity with increasing BSA concentration was demonstrated.

The study indicates that BSA concentration along with excipient added have a decisive impact on lyophilized formulation characteristics, namely prolonged reconstitution time and increased viscosity both represent a main challenge in development of highly concentrated protein formulations.

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Supervisor(s): Mirjam Gosenca Matjaž, Mirjana Gašperlin, Pegi Ahlin Grabnar

OP-22

DOI: 10.14232/syrptbrs.2020.op22

Lipid based nanosystem designed for nose to brain delivery of Alzheimer Disease Drug

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Alzheimer's disease (AD) has been ranked as the most dangerous and prevalent neurodegenerative disease worldwide accompanied by the absence of a fully effective anti-AD medication tightly due to the presence of the blood-brain barrier (BBB). Nose-to-Brain delivery enhances the ability of some drugs to bypass the BBB achieving a therapeutic concentration directly in the brain especially for those with low brain concentrations after a routine delivery. Since the inflammatory process is involved in the pathogenesis of AD and the association of meloxicam with antioxidant properties, the latter could be used in AD management. Unfortunately, poor permeability across the BBB limits its use for the treatment of neurodegenerative disorders in addition to the high rate of plasma protein binding and low apparent distribution volumes. Encapsulation of meloxicam in lipid based nanocarriers, particularly solid lipid nanoparticles (SLN) could be promising for nose to brain delivery due to their biocompatibility, protecting the therapeutic load, while improving its interaction with the olfactory regions.

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OP-23

DOI: 10.14232/syrptbrs.2020.op23

Physicochemical characterization and dissolution studies of terbinafine hydrochloride–cyclodextrin complexes prepared by solvent-free co-grinding

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The purpose of this study was to prepare terbinafine hydrochloride (TER) solid binary systems with amorphous cyclodextrin derivatives (hydroxypropyl-β-cyclodextrin (HPBCD), heptakis(2,6-di-O-methyl)-β-cyclodextrin (DIMEB)) by co-grinding and perform analytical studies. Cyclodextrin–TER complexes were prepared in the 1:1 molar ratio. The products were investigated for both solid phase characterization (differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), hot-humidity stage X-ray powder diffractometry (HOT-XRPD), Raman spectroscopy, Fourier transform infrared spectroscopy (FT-IR)) and dissolution properties (dissolution studies). DSC and XRPD studies indicated that with the increasing grinding time the crystallinity of products gradually decreased, and the products were completely amorphous after 75 minutes of grinding. HOT-XRPD studies were carried out in a wide temperature range and revealed that product containing HPBCD remained amorphous with the increasing temperature, while in the case of DIMEB the complex recrystallized in a different crystalline phase. Raman and FT-IR spectroscopy were used to investigate the molecular interactions between the components. Both products presented a notable improvement in its dissolution rate, and the solubility of TER increased both in simulated gastric and intestinal fluid, depending on the dissolution medium. Co-grinding is a solvent-free method to prepare stable amorphous cyclodextrin complexes and improve solubility and dissolution ratio. This could cause enhanced biopharmaceutical properties of the active ingredients in solid pharmaceutical products.

Supervisor: Zoltán Aigner

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

January 23-24th 2020. Szeged, Hungary

OP-24

DOI: 10.14232/syrptbrs.2020.op24

Cationic nanostructured lipid carriers (cNLCs) as drug delivery systems for miRNA: investigations of formulation and process parameters

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Cationic NLCs represent lipid vesicles bearing cationic lipids on its surface, which leads to electrostatic interactions with negative charges of the nucleic acids such as miRNA and formation of a complex which protect the nucleic acids from the inevitable physicochemical biological impacts within the blood circulation [1]. This study aimed to develop cNLCs in order to obtain the most suitable formulation for further delivery of miRNAs.

cNLCs containing stearylamine, Precirol® ATO 5 and Miglyol® 812 in the lipid phase and different concentrations of Poloxamer® 188 and Tween® 80 in the aqueous phase were prepared by the high-pressure homogenization method. In order to evaluate appropriate process parameters for NLC preparation, different cycle numbers (1-5) and homogenization pressures (500 bar, 650 bar and 800 bar) were tested. Additionally, the influence of the cooling technique was investigated. cNLCs were characterized regarding particle size, particle size distribution, zeta potential, and crystallinity using photon correlation spectroscopy technique and laser diffraction, electrophoretic light scattering, and differential scanning calorimetry, respectively.

The obtained particle size of all formulations was between 80 and 180 nm, and it decreased significantly with the increase of non-ionic surfactant concentration. Furthermore, particle size decreased with the increase of the homogenization cycles. The surface charge value was highly positive in formulations (+32 to +41 mV), demonstrating the successful incorporation of stearylamine onto the nanoparticle surface. However, the cooling technique did not have a significant impact on the particle size of cNLCs.

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Supervisors: Prof. dr. Edina Vranić and Univ.-Prof.dr. Andreas Zimmer

OP-25

DOI: 10.14232/syrptbrs.2020.op25

Fused Deposition Modeling Three-Dimensional Printing (FDM-3DP) of Channelled Tablets with Ketoprofen: Design, Development and Pharmaceutical Evaluation

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Three dimensional printing (3DP) constitutes an innovative approach in the pharmaceutical field with promising potential for the production of personalized medicine, among the available techniques Fused Deposition Modeling (FDM) representing a flexible, simple and cost-effective alternative. The aim of the present study was obtaining and evaluating a channelled tablet model produced by FDM-3DP, using custom made pharmaceutical polymer-based filaments.

Ketoprofen, a nonsteroidal anti-inflammatory drug (NSAID) was selected as the model active pharmaceutical ingredient (API), while polyvinyl alcohol (PVA) represented the matrix forming polymer with thermoplastic behaviour in which the API was included. Feedstock filaments were obtained by hot melt extrusion (HME), followed by FDM-3DP of the tablets. Assessment of the final product included pharmacotechnical characterization and in vitro dissolution studies.

Results demonstrated the feasibility of higher drug loaded, printable filaments. Plasticization was achieved by elevated API content, generating custom made filaments with proper mechanical and rheological properties. In vitro dissolution testing revealed a complete release of the drug up to 4h. Humidity was identified as a factor which could impact the quality of the dosage form, subsequently preventive measures are required during preparation and storage. Production of pharmaceutical dosage forms by a bi-phase technique such as FDM- coupled with HME creates opportunities to improve safety, efficacy and accessibility of medications. FDM-3DP is a versatile tool which could be developed as a single platform qualified to adapt dosage forms based on patients' needs, preferences or individual features.

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Supervisor: Professor Ioan TOMUȚĂ

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

January 23-24th 2020. Szeged, Hungary

OP-26

DOI: 10.14232/syrptbrs.2020.op26

Powder Compressibility Assessment: Manufacturability Classification System vs. SeDeM Expert System

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Manufacturability Classification System (MCS) and SeDeM Expert System have been proposed as mathematical tools facilitating directly compressible tablet formulation [1, 2]. The aim of this work was comparative evaluation of SeDeM and MCS for powder compressibility assessment.

Three active ingredients (ibuprofen, caffeine, paracetamol) and four directly compressible excipients (Ludiflash, Disintequik ODT, Pharmaburst 500, Parteck M200) were evaluated. The investigated powders were characterized with respect to relevant properties determining their flowability and compression behaviour. Experimentally obtained data were mathematically transformed to radii parameters for further evaluation. Subsequently, parameter profile (IPP) and good compression indices (IGC) were calculated as representative measures for powder compressibility assessment.

The results obtained revealed high level of correlation between the IPP and IGC values estimated using both investigated approaches, characterized with the correlation coefficient of 0.9266. While SeDeM expert system is less demanding with respect to the experimental setting required and includes somewhat simpler mathematical processing of the experimental data, MCS provides more detailed insight into material properties influencing powder compression. Furthermore, discriminatory power of the MCS approach appears to be higher since it was able to clearly differentiate poorly performing paracetamol and ibuprofen from caffeine and directly compressible/co-processed excipients (i.e. 3.9 and 6.4 vs. approx. 8.5).

Data obtained can be employed as a proof of concept for further elucidation of flowability and compression behavior of more complex, composite powder samples and multiparticulates.

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Supervisor: prof. dr Jelena Parojčić

OP-27

DOI: 10.14232/syrptbrs.2020.op27

Multivariate modelling for investigating the impact of raw materials and process variability on high drug load immediate release tablets obtained through wet granulation

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The batch-wise wet granulation, drying and tableting are ones of the most widely used technologies in the pharmaceutical industry, with potential impact on both product quality and processability in subsequent steps.
Multivariate data analysis by means of Principal Component Analysis and Projection to Latent Structures models can cope with the highly inter-correlated variables of interest from these processes.
In this study, the multivariate modelling approach was challenged using a historical dataset from 95 industrial-scale batches. This increases the level on inter-correlation even more as the available data are not the result of a planned study.
Batch level models show a good correlation between raw material properties and the evolution of torque values during wet granulation, with 70 % of the Y-variability explained by the model and showing a decent predictability (Q2 = 0,7). The evolution of torque values during wet granulation and the raw material properties are correlated with differences observed in the granulate particle size and disintegration time of core tablets.
Expected correlations were confirmed by this modelling exercise (eg. the influence of active product ingredient particle size), but also new insights were gained regarding the influence of different excipient batches. Despite the relatively tight specification ranges applicable for excipients, the multivariate influence of all raw materials is a good starting point to consider for systematic optimization of disintegration time and tableting performance.

OP-28

DOI: 10.14232/syrptbrs.2020.op28

API – excipient interactions in 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, the 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 the 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 formed between the drug and excipients even in solid state, while investigations during dissolution tests proved that the strength of interactions 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, drug liberation is considerably influenced by the chemical interactions formed between APIs and excipients.

Supervisors: Tamás Sovány, Ildikó Csóka

OP-29

DOI: 10.14232/syrptbrs.2020.op29

Study of Skin Penetration Testing Methods

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Modeling of penetration through the skin is a complex challenge. The success of topical and transdermal therapy is correlated to the techniques used for the evaluation of the preparations, which facilitate the optimization of the skin penetration of the API. Human skin tests give the most relevant information; however, because of the high cost, it is a generally accepted approach to choose simpler methods in the early stages of formulation development. In my PhD work, I study different *in vitro* tests which are used and reliable tool for evaluating products [1, 2]. Although there are many methods for following up skin penetration/permeation the different techniques are not fully equivalent but complement each other. Different types of vertical Franz diffusion cells, the Skin-PAMPA method and Raman mapping have been compared. The models can make rapid screening and faster optimization possible especially in the early stage of development. The selection of the most suitable *in vitro* model should be based on availability, facility of use, cost, and the respective limitations.

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Supervisors: Erzsébet Csányi, Szilvia Berkó

OP-30

DOI: 10.14232/syrptbrs.2020.op30

Nano-crystalline suspensions of novel pyrazoloquinolinones ligand (DK-I-56-1): physicochemical and in vivo pharmacokinetic and behavioural characterization

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Very low solubility in water and oils (<10 μg/ml) of DK-I-56-1 (7-methoxy-2-(4-methoxy-d3-phenyl)-2,5-dihydro-3H-pyrazolo[4,3-c]quinolin-3-one), the new drug candidate from the group of deuterated pyrazoloquinolinones [1], was the reason for investigation of nano-crystalline suspensions (nanosuspensions) as prospective carriers. Nanosuspensions are dispersions of nanocrystals with submicron size stabilized by different surfactants and/or polymeric stabilizers [2]. In this research, formulation and comprehensive characterisation of DK-I-56-1 nanosuspensions were carried out. Nanosuspensions stabilized by polysorbate 80 alone or in combination with poloxamer 188, poloxamer 407 or d-α-Tocopheryl polyethylene glycol 1000 succinate were prepared by small scale media milling technique. All formulations had particle size 208.7 – 250.6 nm, polydispersity index <0.250 and zeta potential around -20 mV, and were stable for three weeks. According to thermal and X-ray diffraction analysis DK-I-56-1 remained in crystalline state in all samples. Results from biodistribution studies in mice after intraperitoneal administration showed high plasma DK-I-56-1 levels after nanosuspension administration (AUC values for nanosuspension, suspension and solution: 6770.35±770.69; 966.01±58.10; 10228.58±1037.23 ngh/ml, respectively). Brain availability was higher after nanosuspension compared to solution, while concentration profile after suspension showed bimodal characteristics. In *in vivo* behavioural (spontaneous locomotor activity) tests hyperlocomotion was observed after nanosuspension administration compared to saline or placebo ($F(2,31)=7.126$, $p<0.01$), while placebo was not behaviourally active compared to saline ($p=0.289$). In conclusion, DK-I-56-1 nanosuspensions with short term stability could be prepared and should be investigated as promising carrier for preclinical investigation.

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Supervisor(s): Snežana Savić, Miroslav Savić

OP-31

DOI: 10.14232/syrptbrs.2020.op31

Formulation and investigations of lysozyme nanoparticle

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Lysozyme is an alkaline enzyme found mostly in plants, animals, and microbes. It can damage bacterial cell walls by catalysing the hydrolysis of 1,4-b-linkages between muramic acid and N-acetyl glucosamine in mucopolysaccharides and is present in various human tissues and secretions. Therefore, it is widely used as a cell-disrupting and potent anti-bacterial reagent. It is also in high demand due to its unique pharmacological functions such as anti-inflammatory, antiviral, antiseptic, and antineoplastic activities [1]. It is naturally occurring, non-toxic, and easy to digest and absorb.

Nanoparticles can change and improve the properties of proteins such as mechanical, degradable properties and they can protect and control release of the bioactive substances as a delivery system [2].

For the purpose of this research, we carried out pre-formulation experiments by varying factors such as the concentration of the lysozyme and precipitating agent and the pH by using the factorial design method. Based on these variations, different formulations of the lysozyme and precipitating agent were prepared, tested and optimised and the resulting nanoparticles were comprehensively characterised.

Furthermore, Statistica analysis measurements were carried out using the different values for the lysozyme concentration and the sodium sulphate amounts which served as determinant factors for the particle size of the lysozyme nanoparticle solution.

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Supervisor: Ildikó Csóka

Acknowledgement

Ministry of Human Capacities, Hungary grant TUDFO/47138-1/2019-ITM is acknowledged.

OP-32

DOI: 10.14232/syrptbrs.2020.op32

Low-energy nanoemulsions for curcumin delivery: investigation of the interfacial phenomena in the colloidal system and peculiarities important for biological performances

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Low-energy nanoemulsions (LE-NEs) represent novel and multifunctional drug carriers [1]. Curcumin, a powerful pleiotropic molecule, was used as a model active ingredient in this study. However, due to physicochemical instability, poor solubility and low targeting efficacy, its potentials are still beyond the reach [2]. Therefore, the aim was to investigate developed LE-NEs as promising vehicles for curcumin delivery, linking microstructural properties of the carrier to delivery and biological performance.

After structural investigation, applying several physicochemical techniques (photon correlation spectroscopy, differential scanning calorimetry, atomic force microscopy, electron paramagnetic resonance spectroscopy), efficacy of curcumin and curcumin-loaded LE-NEs was assessed in terms of antioxidant activity and in biological assays with several cell lines (Fem-X, HeLa, MRC-5).

All developed formulations had mean droplet diameter below 150nm, with narrow distribution. It was demonstrated that curcumin interacts with the interfacial region of the LE-NE, being a part of the surfactant layer, closer to the lipophilic region. Scavenging activity of curcumin-loaded LE-NEs was high, remaining unaltered after several months of storage. Encapsulation in the LE-NE enhanced its safety profile, providing significant cytotoxicity towards HeLa and Fem-X compared to the effect towards MRC-5 (IC50=22.89±2.09; 37.87±7.09 and 67.72±0.4μg/ml, respectively). After the cell cycle analysis, it was proved that the cycle arrest of the cancer cells mostly happened in the subG1 and G2/M phase, underlining the ability of curcumin to interact with numerous cellular signaling pathways.

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Supervisor: prof. Snežana Savić

OP-33

DOI: 10.14232/syrptbrs.2020.op33

Investigation of semi-solid in situ film-forming systems with QbD approach

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The development of dermal preparations is a great challenge to provide good penetration through the skin because of the barrier function of stratum corneum. Film forming systems (FFSs) are new alternative drug delivery systems which can increase the impact of dermal preparations.

The aim of my research work was to develop dermally applicable semi-solid in situ FFSs containing silicones, which form a film on the skin, with appropriate mechanical properties Silicones were used in the systems because of their “silky-touch” and protective effects to improve the quality of FFSs. FFSs were developed and investigated using the Quality by Design (QbD) approach. During the initial risk assessment, critical attributes were distinguished and measured. These critical quality attributes (CQAs) were skin adhesion, film flexibility and burst strength, film appearance, film integrity and the drying time of the semi-solid system. Critical material parameters (CMAs), namely the type of silicones, film forming excipients, drying excipients, and viscosity enhancing excipients were also found.

The results showed that the silicone content had a great effect on the FFSs. They had an influence on the mechanical properties of the films, and on the drying time. The investigation of the drying mechanism showed promising results because of the silicon content.

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Supervisor(s): Szilvia Berkó, Erzsébet Csányi

Acknowledgments:

This work was supported by the Gedeon Richter’s Talentum Foundation (Gyömrői street 19-21., Budapest, Hungary, 1103), the construction EFOP 3.6.3-VEKOP-16-2017-00009, and Supported by the ÚNKP-19-3-SZTE-141 New National Excellence Program of the Ministry for Innovation and Technology.”

OP-34

DOI: 10.14232/syrptbrs.2020.op34

Effect of Processing Conditions and Material Attributes on the Design Space of Lysozyme Pellets Prepared by Extrusion/Spheronization

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The formulation of macromolecular drugs such as proteins into stable solid dosages represents a challenging goal as a result of the mechanical attrition and thermal stress involved during their production [1].

This study aimed to investigate the impact of the material attributes and processing parameters on the quality of the prepared pellets containing a macromolecular drug. Spray-dried and lyophilized lysozymes were used as a model protein, crystalline and spray-dried mannitol were involved as conformation stabilizers [2] and microcrystalline cellulose served as pellet former. The experiments were conducted according to 2^3 full factorial design. Kneading was performed in the high shear granulator equipped with seven temperature and relative humidity (RH) sensors (Opulus, Hungary). The obtained granules were extruded at different rates, and the extrudates were spheronized at a fixed rate.

The dried samples were investigated for the enzyme activity and physical properties. It was found the material attributes have a potential effect on biological activity and pellet properties, as they demonstrated different thermal responses upon the applied mechanical stresses; lysozyme showed considerably good stability towards the applied mechanical stress and generated heat. It was concluded that the instrumented chamber represents a novel means for the online monitoring of temperature and RH%. Besides, screening of the formulation excipients is a key factor for the successful production of multiparticulates containing protein.

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Supervisors: Katalin Kristó, Géza Regdon jr., Tamás Sovány

OP-35

DOI: 10.14232/syrptbrs.2020.op35

Treatment of the off-periods of Parkinson's disease with levodopa and its derivative

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Levodopa is the gold standard API for the treatment of Parkinson's disease. It is mainly administrated per os and absorbed in the small intestines. The bioavailability of the levodopa is low and alternates because of numerous disadvantages belonging to this route, for example fluctuating gastric akinesia, high first-pass effect. When the levodopa concentration is low, the symptoms of off-periods appear. The intranasal route is an alternative possibility to treat the off-periods [1].

Unlike the levodopa, the melevodopa can be absorbed in the stomach because it exists in the non-ionized form at low pH, additionally, its solubility is much higher, therefore the bioavailability can become higher. As it can be absorbed in the stomach, the onset can be increased and the gastric akinesia can be eliminated.

The Syloid XDP 3050 –mesoporous silica – can adsorb a remarkable amount of compounds and the dissolution properties of the APIs can be regulated.

During work, preliminary experiments were executed to prepare drug delivery systems with fast dissolution. In the first part of the study, levodopa-containing nasal powder formulations were prepared with co-milling using excipient. In this study melevodopa was adsorbed on the surface of the Syloid to prepare tablet formulations to achieve a fast dissolution in the gastric medium. Physicochemical and *in vitro* studies were performed with the products.

Summarizing, drug delivery systems for the treatment of the off-periods of Parkinson's disease were prepared. A comparison of the pharmacokinetic parameters of the formulations is planned.

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Supervisor: Rita Ambrus

Acknowledgement

Ministry of Human Capacities, Hungary grant 20391-3/2018/FEKUSTRAT and EFOP 3.6.3-VEKOP-16-2017-00009 are acknowledged.

OP-36

DOI: 10.14232/syrptbrs.2020.op36

Investigation of bottom-up prepared nanostructures

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Generally, by systemic administration the low oral bioavailability can be caused by poor solubility. Therefore, increasing the water solubility of active pharmaceutical ingredients (API) enhances the oral bioavailability of drugs. Various nanonization techniques can be used to achieve increased solubility. Nanofabrication can be classified as bottom-up and top-down methods. The bottom-up strategy is considered more advantageous than the top-down approach because it has a better chance of producing more homogenous nanostructures. Electrospun nanofibers and nanocapsules could be examples of the bottom-up approach. Nanofibers can be prepared by using electric force during the electrospinning procedure. The amorphous form and the large surface area prove the increased water solubility of the API [1-2]. Nanocapsules are vesicular systems that carry the API inside a cavity surrounded by a polymeric membrane. The advantages of the nanocapsules are reducing the toxicity and improving the stability of the drugs and the high drug encapsulation efficiency.
Our aim is enhancing the water solubility and the dissolution rate of different APIs by bottom-up nanofabrication methods such as electrospinning and nanoprecipitation. As a plan, the investigation of the prepared electrospun nanofibers and the nanocapsules covers the micrometric and physicochemical properties, *in vitro* dissolution of the API. The final purpose of the work is to develop preparation protocols for electrospinning and nanoencapsulation technology.

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Supervisor: Rita Ambrus

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

January 23-24th 2020. Szeged, Hungary

OP-37

DOI: 10.14232/syrptbrs.2020.op37

PEGylation and formulation strategies of antimicrobial peptides and proteins development

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The potential of antimicrobial peptide and protein agents has yet to be concerned owing to the many unresolved problems including low bioavailability, high manufacturing cost and toxicity concerning their delivery to the target site [1].
Novel chemical modification approaches as well as strategies for delivery of proteins and peptides offer several opportunities to overcome these barriers. However, these approaches hide several risks. This study presents a Quality by Design (QbD) based peptide and protein modification and formulation design. Analyses the potential risks in the peptide PEGylation process through the example of PGLa and on the other hand, the effective delivery of proteins with antimicrobial activity was accomplished through the example of lysozyme in a novel formulation strategy as layer-by-layer polyelectrolyte core-shell nanoparticle [2]. The precipitation method was applied for the formulation of core and the second step was the layering of polymers according to the factorial design. The particle size, zeta potential and enzyme activity were the optimization parameters.

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Supervisor(s): Dr.Ildikó Csóka, Dr.Gerda Szakonyi

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

January 23-24th 2020. Szeged, Hungary

OP-38

DOI: 10.14232/syrptbrs.2020.op38

Development of Inhalable Chitosan nano system conjugated with Hyaluronic acid for treatment of Tuberculosis

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Tuberculosis is the global health burden and the conventional therapies are unable to deliver the drug to the alveolar macrophages, where the causative agent (Mycobacterium tuberculosis) resides and replicates. The potential of chitosan polymer conjugated with hyaluronic acid was exploited for the targeted drug delivery via inhalation [1]. Nano mediated drug delivery vehicle was synthesized using ionic gelation for the active targeting of the alveolar macrophages. Dry powder inhalers (DPI) comprised of biodegradable polymeric nanocarriers with adequate aerodynamic profile, drug release and biocompatibility is a major challenge for pulmonary drug delivery. Quality by design approach was therefore employed to critically evaluate the risk assessment profile to enhance the product optimization [2]. Physicochemical tests including FT-IR, DSC, TGA, XRPD, SEM, size analyses and aerodynamic characterization provided useful data about compatibility and stability of the nanoparticular system. Nano DPI might hence improve the drug bioavailability by the reduction in dosing frequency and toxicity [3].

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Supervisor: Dr. Rita Ambrus

OP-39

DOI: 10.14232/syrptbrs.2020.op39

Significance of QbD in design and development of coated liposomes for nose to brain delivery

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Nose to brain delivery is noninvasive, direct and more effective route of administration than other invasive treatments that comes with many pitfalls. In this study quality by design (QbD) and risk assessment (RA) strategy was used for development of novel optimized liposomes encapsulated with propyl gallate (PG) for nose to brain delivery. This risk focused research helps to define target product profile, critical quality and process parameters were also analysed. The application of QbD helped in the box behnken design-based liposome preparation by the novel direct pouring method (DPM). Compatibility studies (FTIR, DSC, XRPD, TGA) were performed for materials used and for lyophilized optimized formulations. The prepared optimized liposomal preparations were characterized (particle size, polydispersity index, and surface charge). The surface morphology was also evaluated to confirm the precision of the RA and critical parameters based on QbD prediction. The following study verify that in formulation of liposomes the RA startegy has significant importance. The developed optimized formulation via this novel approach results in maximum encapslation efficiency and minimum particle size. The implimentation of this novel QbD deisgn and models can assists in, to develop the rationalize liposomal formulation for nose to brain delivery.

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Supervisor: Ildikó Csóka

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

January 23-24th 2020. Szeged, Hungary

OP-40

DOI: 10.14232/syrptbrs.2020.op40

Development and characterization of sodium alginate polymer film as a buccal mucoadhesive drug delivery system

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Nowadays oral mucoadhesive systems have an increasingly greater role in the pharmaceutical industry. These systems can avoid the first-pass effect because they allow drugs to be absorbed directly into the systemic circulation and they have further advantages [1, 2]. The aim of this work is to formulate and evaluate polymer films of different composition that are able to bind to the buccal mucosa.

Sodium alginate and hydroxypropyl methylcellulose (HPMC) were used as polymer, glycerol was the plasticizer, and cetirizine dihydrochloride served as active pharmaceutical ingredient. Mucin was used in the mucoadhesion tests. The polymer film was prepared at room temperature by solvent casting method. The polymer films contained different amounts of sodium alginate, HPMC and glycerol, but the same amount of cetirizine dihydrochloride. The thickness of the films was examined with a screw thread micrometer (Mitutoyo, Japan), the tensile strength and mucoadhesive force was tested with a laboratory constructed device. The physical and chemical properties of the films were investigated with FT-IR (Avatar 330 ThermoScientific, USA) and thermal analysis (Mettler Toledo, Switzerland). Surface free energy was examined by an optical contact angle-measuring apparatus (OCA20, DataPhysics, Germany). The dissolution of the active substance was tested by an ErwekaDT700 dissolution tester and the sample was measured by a UV spectrometer. The results showed that the material exerts a remarkable effect on the properties of polymer films, and the active substance showed homogeneous distribution.

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OP-41

DOI: 10.14232/syrptbrs.2020.op41

Influence of process parameters on supercritical carbon dioxide extraction of cannabidiol from *Cannabis sativa* L. aerial parts

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Hemp (*Cannabis Sativa* L.) has multiple applications in the industry for the production of fabrics, paper and construction materials. Today, there is an increasing interest in its application for medical purposes, as opposed to its opiate activity. Hemp has more than 480 compounds: cannabinoids, terpenoids, flavonoids, noncannabinoid phenols, hydrocarbons, nitrogen-containing compounds, carbohydrates [1].

The influence of pressure (100 - 300 bar) and temperature (40 ^{o}C - 60 ^{o}C) on supercritical carbon dioxide extraction of aerial parts of hemp in terms of cannabidiol (CBD) was examined. The CBD content was in the range from 0.0071 to 0.0896 g/extract for the pressure of 100 bar, from 0.1341 to 0.2587 g/extract for the pressure of 200 bara and from 0.1797 to 0.3103 g/extract for the pressure of 300 bar. Depending on the pressure used, the temperature had a different effect. At the pressure of 100 bar increasing the temperature leads to decrease in the extraction of CBD. At pressures of 200 and 300 bar increasing the temperature to 50 °C amount of extracted CBD decreased, while further increasing the temperature to 60 °C amount of extracted CBD results in a slight increase. The highest content of CBD was in the extract obtained at a pressure of 300 bar and temperature of 40 °C.

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