

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

19-21 January, 2022

Book of Abstracts



University of Szeged







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

January 19-21, 2022 - Szeged, Hungary

### Greetings



On behalf of the Scientific Committee, I am very pleased to welcome the participants of the 4th 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.

This is the fourth time that the Symposium has been organized by the Institute of Pharmaceutical Technology and Regulatory Affairs and the Foundation for the Development of Pharmacy Education, University of Szeged.

The aim of the program is unchanged to get to know the work of Hungarian and foreign 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.

We are past three successful symposia showing the need for this event for young researchers, so we continue this series and want it to become a tradition over time.

We are delighted to welcome PhD students and cooperation partners from 13 universities in 12 countries (Bosnia and Herzegovina - University of Sarajevo; Bulgaria - Medical University of Plovdiv; Czech Republic - Charles University; Estonia - University of Tartu; Germany - Heinrich-Heine University; Hungary - University of Szeged; Pakistan - Quaid-i-Azam University, Islamabad; Poland - Medical University of Gdansk; Romania - Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca; Serbia - University of Belgrade; University of Novi Sad; Slovenia - University of Ljubljana and Spain - University of Santiago de Compostela). The program includes 32 oral and 15 flash presentations. The topics and research results will be presented in 11 sections. The flash format, the presentation of 3-5 minutes videos, will be a new highlight of this symposium.

The current 4th Symposium will be held in hybrid form (online and contact) in view of the COVID pandemic. This is a three-day event provides a good opportunity to discuss the new developments and the future directions of the pharmaceutical sciences.

I am looking forward to having a successful conference with fruitful discussions.

*Prof. emer. Piroska Szabó-Révész*  
*Head of Scientific Committee*

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

19-21 JANUARY 2022

SZEGED, HUNGARY



## General Information

**Date:** 19-21 January 2022

**Location:** Hybrid (University of Szeged, Faculty of Pharmacy, and online MS Teams)

**Congress Topics:** Pharmaceutical technology, biotechnology and regulatory science

**Types of presentations:**

1. Oral presentation (10 min + 5 min discussion)
2. Flash presentation (3-5 min, pre-recorded)

**Submission of abstracts:** [gytfi.phd.pharm@szte.hu](mailto:gytfi.phd.pharm@szte.hu)

**DOI:** [10.14232/syrptbrs.2022.af](https://doi.org/10.14232/syrptbrs.2022.af)

**Edited:** Luca Éva Uhljar and Bence Sipos

**Image:** Balázs Attila Kondoros

**Photos:** Tamás Sovány

## Contacts

### President of the Symposium

Prof. Dr. Ildikó Csóka  
Head of Institute

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### Organiser

Institute of Pharmaceutical Technology  
and Regulatory Affairs  
University of Szeged  
Hungary

### Head of Organising Committee

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### Co-organiser

Foundation for the Development of  
Pharmacy Education at the University  
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## IV. Symposium of Young Researchers on Pharmaceutical Technology, Biotechnology and Regulatory Science

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### Committees

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#### Head of the Organizing Committee

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

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### Short Program

Wednesday, 19<sup>th</sup> January – 12:30-16:30 CET

11:00 - 12:30 Registration and Welcome Reception  
12:30 - 14:15 **Opening Ceremony and Plenary Session**  
14:15 - 14:30 Coffee Break  
14:30 - 15:30 **Session 1**  
15:30 - 15:45 Break  
15:45 - 16:30 **Session 2**  
19:00 - **Networking event - in person**

Thursday, 20<sup>th</sup> January – 9:00-15:45 CET

9:00 - 10:00 **Session 3**  
10:00 - 10:15 Coffee break  
10:15 - 11:15 **Session 4**  
11:15 - 11:30 Break  
11:30 - 12:15 **Session 5**  
12:15 - 13:30 Lunch break  
13:30 - 14:30 **Session 6**  
14:30 - 14:45 Break  
14:45 - 15:45 **Session 7**  
19:00 - **Game Night - online**

Friday, 21<sup>st</sup> January – 9:00-14:45 CET

9:00 - 10:00 **Session 8**  
10:00 - 10:15 Coffee break  
10:15 - 11:15 **Session 9**  
11:15 - 11:30 Break  
11:30 - 12:15 **Session 10**  
12:15 - 13:30 Lunch break  
13:30 - 14:30 **Session 11**  
14:30 - 14:45 **Closing Ceremony**





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

January 19-21, 2022 - Szeged, Hungary

### Schedule

Wednesday, 19<sup>th</sup> January – 12:30-16:30 CET

**11:00-12:30**    **Registration and Welcome Reception**

Location: University of Szeged, Faculty of Pharmacy  
6 Eötvös Street, Szeged, Hungary

**12:30-13:00**    **Opening Ceremony:**

**Prof. Dr. Ildikó Csóka** (President of the Symposium, Head of Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged)

**Prof. Dr. Piroska Szabó-Révész** (Head of the Scientific Committee, University of Szeged)

**Dr. Péter Mezei** (Director of the Doctoral Institute, University of Szeged)

**Prof. Dr. István Zupkó** (Dean of Faculty of Pharmacy, University of Szeged)

**Prof. Dr. Zsolt Szakonyi** (Secretary general of the Doctoral School of Pharmaceutical Sciences, University of Szeged)

**13:00-14:15**    **Plenary Session:**

**Dr. Krisztián Fodor** (Head Regulatory Science and Patient Safety at Gedeon Richter Plc.)

Innovation & regulation: Hand in hand

**Dr. Senka Vidović** (Assistant Professor at Faculty of Technology, University of Novi Sad)

Supercritical carbon dioxide extraction: principle and applications in bioactive compound isolation

**14:15-14:30**    **Coffee break**

**14:30-15:30**    **Session 1 – Chairs: Prof. Dr. Peter Kleinebudde, Dr. Géza Regdon jr.**

**OP-1 – 14:30-14:45**    **Mirjana Sulejmanović, Senka Vidović, Naffati Abdulhakim, Nataša Nastić, Aleksandra Gavarić**

Can we turn Arctostaphylos uva-ursi L. tea factory waste into herbal extracts for pharmaceutical formulations?

**OP-2 – 14:45-15:00**    **Krisztián Pamlényi, Géza Regdon jr., Dániel Nemes, Ildikó Bácskay, Katalin Kristó**

Stability and permeability properties of sodium alginate buccal films



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- OP-3 – 15:00-15:15**      **Tamás Kiss**, Rita Ambrus, Mohamed M. Abdelghafour, László Janovák, Mária Budai-Szűcs, Ágota Deák, Gábor Katona
- Synthesis and investigation of a mucoadhesive chitosan derivative for intranasal drug delivery
- OP-4 – 15:15-15:30**      **Slađana Krivošija**, Zorana Mutavski, Senka Vidović, Nataša Nastić
- Intensification of anthocyanin extraction from Sambucus nigra fruits using ultrasonic probe: Effect of factors, and comparison with conventional extraction approach
- 15:30-15:45**      **Break**
- 15:45-16:30**      **Session 2** – **Chairs: Dr. Senka Vidović, Dr. Rita Ambrus**
- FP-1 – 15:45-15:50**      **Ivana Vasiljević**, Jelena Parojčić
- An investigation into multiparticulate units printability by selective laser sintering
- FP-2 – 15:50-15:55**      **Merima Sirbubalo**, Tamás Sovány, Katalin Kristó, Géza Regdon jr, Edina Vranić
- Development of solid self-nanoemulsifying drug delivery systems (s-SNEDDS) for oral delivery of lysozyme
- FP-3 – 15:55-16:00**      **Maryana Salamah**, György Tibor Balogh, Gábor Katona
- Improving the bioavailability of favipiravir by using human serum albumin nanoparticles
- FP-4 – 16:00-16:05**      **Mila Kovačević**, Ilija German Ilić, Alenka Zvonar Pobirk
- The influence of SMEDDS composition and the water ratio in granulation dispersion on attributes of granules prepared by wet granulation
- FP-5 – 16:05-16:10**      **Ranim Saker**, Géza Regdon jr., Tamás Sovány
- Preparation of functionalized titanate nanotubes to improve toxicological profile and bioavailability
- Q&A – 16:10-16:30**
- 19:00-**      **Networking event**
- Location: Atrium Café (9 Kárász Street, Szeged)





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### Thursday, 20<sup>th</sup> January – 9:00-15:45 CET

**9:00-10:00**      **Session 3 – Chairs: Dr. Bissera Pilicheva, Dr. Szilvia Berkó**

**OP-5 – 9:00-9:15**      **Zsófia Németh**, Reza Semnani Jazani, Bence Sipos, Dorina Gabriella Dobó, Edina Pallagi, Ildikó Csóka

Risk-based optimization of liposome-based nano-carrier systems

**OP-6 – 9:15-9:30**      **Reihaneh Manteghi**, Katalin Kristó, Ildikó Csóka

Optimization of layering technique and the secondary structure analysis during formulation of nanoparticles containing lysozyme by Quality by Design approach

**OP-7 – 9:30-9:45**      **Patrícia Varga**, Rita Ambrus, Piroska Szabó-Révész, Dávid Kókai, Katalin Burián, Zsolt Bella, Ferenc Fenyvesi, Csilla Bartos

Preparation and investigation of meloxicam potassium containing cyclodextrin nanoparticles intended for nasal application

**OP-8 – 9:45-10:00**      **Balázs Attila Kondoros**, Lucio Giuseppe Sanzeri, Maria Cristina Bonferoni, Milena Sorrenti, Ildikó Csóka, Rita Ambrus

Ternary systems of terbinafine hydrochloride inclusion complexes: preparation, solid-state characterization, dissolution studies

**10:00-10:15**      **Coffee break**

**10:15-11:15**      **Session 4 – Chairs: Dr. Livia Adalbert, Dr. Hussain Ali**

**OP-9 – 10:15-10:30**      **Eleni Panoutsopoulou**, Georgios Paraskevopoulos, Jarmila Zbytovská, Kateřina Vávrová

Solubility and skin permeability of imiquimod in liposome-dendrimer systems

**OP-10 – 10:30-10:45**      **Fanni Falusi**, Anita Kovács, Szilvia Berkó

Formulation and investigation of the effect of polymers on dermal foam properties using the QbD approach

**OP-11 – 10:45-11:00**      **Sabrina Berkenkemper**, Lenny Paola Espinoza Luna, Peter Kleinebudde

Comparison of two commonly used compression analyses for in-die and out of die performance

**OP-12 – 11:00-11:15**      **Tsenka Grancharova**, Stanislava Simeonova, Bissera Pilicheva, Plamen Zagorchev

Derivation of appropriate parameters for photothermal therapy, mediated by iron oxide nanoparticles



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**11:15-11:30 Break**

**11:30-12:15 Session 5 – Chairs: Dr. Katalin Kristó, Dr. Gábor Katona**

**FP-6 – 11:30-11:35 Erna Turković, Jelena Parojčić**

An investigation into relationship between thin films mechanical and rheological properties

**FP-7 – 11:35-11:40 Boglárka Szalai, Mária Budai-Szűcs, Orsolya Jójárt-Laczkovich**

Design and optimization of dexamethasone containing in situ gelling mucoadhesive eye drops

**FP-8 – 11:40-11:45 Lamija Hindija, Jasmina Hadžiabdić, Edina Vranić, Ognjenka Rahić**

Improvement of dimenhydrinate solubility by complexation with  $\beta$ -cyclodextrin

**FP-9 – 11:45-11:50 Radka Boyuklieva, Bissera Pilicheva**

Nanocarrier-mediated nose-to-brain drug delivery for Parkinson's disease

**FP-10 – 11:50-11:55 Reza Semnani Jazani, Zsófia Németh, Dorina Gabriella Dobó, Ildikó Csóka**

Pharmaceutical study of essential oil-loaded liposomal formulations

**Q&A – 11:55-12:15**

**12:15-13:30 Lunch break**

**13:30-14:30 Session 6 – Chairs: Dr. Zsófia Németh, Dr. Urve Paaver**

**OP-13 – 13:30-13:45 Ana Baumgartner, Odon Planinšek**

Development and optimisation of a novel free-flowing and compressible co-processed excipient containing mesoporous silica and isomalt for the production of solid dispersions

**OP-14 – 13:45-14:00 Yousif H-E. Y. Ibrahim, Gábor Katona, Géza Regdon jr., Tamás Sovány**

Development and characterization of lysozyme loaded gum arabic as innovative oral films

**OP-15 – 14:00-14:15 Cristina Barbălată, Alina Porfire, Lucia Tefas, Laurian Vlase, Ioan Tomuță**

The implementation of the QbD concept in the development of lipobeads loaded with gemcitabine: the screening study

**OP-16 – 14:15-14:30 Petra Party, Rita Ambrus**

Formulation and investigation of ibuprofen containing inhalable nanocrystals to treat cystic fibrosis

**14:30-14:45 Break**



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**14:45-15:45**     **Session 7** – Chairs: Prof. Małgorzata Sznitowska, Dr. Tamás Sovány

- OP-17** – 14:45-15:00     **Nina K. Grilc**, Julijana Kristl, Tomaž Rijavec, Aleš Lapanje, Špela Zupančič  
Nanofibers with probiotics combination for treatment of periodontal disease
- OP-18** – 15:00-15:15     **Amina Tucak-Smajić**, Edina Vranić, Andreas Zimmer  
Formulation and characterization of cationic nanoemulsions as carriers for microRNA
- OP-19** – 15:15-15:30     **Sandra Robla**, Jose Manuel Ageitos, Rita Ambrus, Noemi Csaba  
Pollen-based microcapsules for pulmonary delivery of anti-tuberculosic drugs
- OP-20** – 15:30-15:45     **Mahira Zeeshan**, Hussain Ali  
Design of ligand anchored polymeric nanoparticles for potential targeted drug delivery in intestinal inflammation

**19:00-**     **Online games**



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### Friday, 21<sup>st</sup> January – 9:00-14:45 CET

**9:00-10:00**      **Session 8 – Chairs: Dr. Alina Porfire, Dr. Noemi Csaba**

**OP-21 – 9:00-9:15**                      **Stanislava Simeonova**, Tsenka Grancharova, Plamen Zagorchev, Bissera Pilicheva

Casein-coated iron oxidemagnetic nanoparticles–preparation and evaluation for possible application in hyperthermia treatment

**OP-22 – 9:15-9:30**                      **Réka Szoleczky**, Mária Budai-Szűcs, Anita Kovács

Analytical Quality by Design (AQbD) approach to the development of in vitro release test for topical hydrogel

**OP-23 – 9:30-9:45**                      **Katarzyna Krzeminska**, Małgorzata Sznitowska

Stability studies of cefuroxime loaded self-emulsifying drug delivery systems for ocular administration

**OP-24 – 9:45-10:00**                      Eleesha Sana, Mahira Zeeshan, Qurat Ul Ain, Ashraf Ullah Khan, Irshad Hussain, Salman Khan, Elise Lepeltier, **Hussain Ali**

Preparation and characterization of curcumin-loaded transfersomal gel for the treatment of rheumatoid arthritis

**10:00-10:15**      **Coffee break**

**10:15-11:15**      **Session 9 – Chairs: Prof. Jelena Parojčić, Dr. Orsolya Jójárt-Laczkovich**

**OP-25 – 10:15-10:30**                      **Črt Dragar**, Nives Belcar, Sebastjan Nemeč, Slavko Kralj, Mirjana Gašperlin, Petra Kocbek

Electrospinning as a novel method for drying iron-oxide-based magnetic nanoparticle dispersions

**OP-26 – 10:30-10:45**                      **Nikolett Kis**, Maria Gunnarsson, Emma Sparr, Anita Kovács, Szilvia Berkó

The effects of chemical permeation enhancer glycols on the skin

**OP-27 – 10:45-11:00**                      **Bence Sipos**, Ildikó Csóka, Gábor Katona

Spray-dried indomethacin-loaded polymeric micelles for the improvement of peroral bioavailability

**OP-28 – 11:00-11:15**                      **Fakhara Sabir**, Gábor Katona, Zsuzsanna Schelz, Bence Sipos, Muhammad Naveed, István Zupkó, Ildikó Csóka

Lomustine and n-propyl gallate co-encapsulated liposomes for targeting glioblastoma multiforme via intranasal route: ex vivo permeability and in vitro cell line study

**11:15-11:30**      **Break**



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**11:30-12:15**     **Session 10** – Chairs: **Dr. Krisztina Ludasi, Dr. Georgios Paraskevopoulos**

- FP-11** – 11:30-11:35     **Heba Banat**, Ildikó Csóka, Rita Ambrus  
Formulation of a combined dry powder inhalation therapy for cystic fibrosis
- FP-12** – 11:35-11:40     **Luca Éva Uhljar**, Norbert Radacsi, Rita Ambrus  
Comparison of single-needle and nozzle-free electrospinning methods
- FP-13** – 11:40-11:45     **Azza A.K. Mahmoud**, Yousif H-E.Y. Ibrahim, Géza Regdon jr., Katalin Kristó  
Effect of Process Conditions and Parameters on Low-Dose Drug Uniformity Formulated as Pellets
- FP-14** – 11:45-11:50     **Martin Cseh**, Gábor Katona, Ildikó Csóka  
Additive manufacturing in the service of personalized medicines – opportunities and future plans
- FP-15** – 11:50-11:55     **Sandra Aulia Mardikasari**, Ildikó Csóka, Katona Gábor  
Development of in situ mucoadhesive-thermosensitive gel of amoxicillin for intranasal delivery

**Q&A** – 11:55-12:15

**12:15-13:30**     **Lunch break**

**13:30-14:30**     **Session 11** – Chairs: **Prof. Pirooska Szabó-Révész, Prof. Mirjana Gašperlin**

- OP-29** – 13:30-13:45     **Alharith A. A. Hassan**, Katalin Kristó, Tamás Sovány  
Designing of buccal mucoadhesive films as a drug delivery platform for biopharmaceuticals: a preformulation study
- OP-30** – 13:45-14:00     **Hussein Akel**, Gábor Katona, Ildikó Csóka  
In vitro quantitative comparison study of insulin SLNs and PLGA NPs as potential carriers for the brain delivery of intranasal insulin
- OP-31** – 14:00-14:15     **S P Yamini Kanti**, Ildikó Csóka, Livia Adalbert, Orsolya Jójárt-Laczkovich  
Modelling urinary catheters with innovative approaches for patient's using QbD & 3D bioprinting
- OP-32** – 14:15-14:30     **Mahwash Mukhtar**, Noemi Csaba, Sandra Robla, Rita Ambrus  
Mannosylated chitosan-based pulmonary drug delivery system for targeting macrophages

**14:30-14:45**     **Closing Ceremony**



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# **Abstracts**

## ***Oral presentations***





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

January 19-21, 2022 - Szeged, Hungary

DOI: [10.14232/syrptbrs.2022.13](https://doi.org/10.14232/syrptbrs.2022.13)

### **Designing of buccal mucoadhesive films as a drug delivery platform for biopharmaceuticals: a preformulation study**

Alharith A. A. Hassan, Katalin Kristó, Tamás Sovány

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



Oral route has been extensively studied for the delivery of biologics by virtue of its superiority over the parenteral route in terms of patient's convenience and compliance. Within this scope, buccal mucoadhesive films represent a potential delivery platform for such therapies. However, biological drugs are delicate materials which need careful considerations and manipulation to prevent their degradation and keep their biological activity during manufacturing and administration.

This work aims to investigate different factors that affect the formulation of peptide-loaded buccal mucoadhesive films prepared by film casting method. Quality by design tools have been employed to explore a variety of process parameters and material attributes that affects the quality of buccal films loaded with lysozyme as a model peptide. Based on the literature and previous experience, chitosan has been selected as a film forming polymer and the effects of seven factors were tested utilising Plackett-Burman screening design. Those factors involve the grade of chitosan, concentration of the polymer, concentration of citric acid, type and concentration of the plasticizer, the amount of the formula per plate and the applied drying temperature. Within this setting, two main responses have been selected for the evaluation, namely; the mucoadhesivity and tensile strength of the films. The output of this work will be employed in the subsequent steps of developing and optimization using one of the optimization designs of experiments.

#### References

1. Montenegro-Nicolini M, Morales JO. Overview and Future Potential of Buccal Mucoadhesive Films as Drug Delivery Systems for Biologics. AAPS PharmSciTech. 2017 Jan;18(1):3–14.



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DOI: [10.14232/syrptbrs.2022.14](https://doi.org/10.14232/syrptbrs.2022.14)

### Formulation and characterization of cationic nanoemulsions as carriers for microRNA

Amina Tucak-Smajić<sup>1</sup>, Edina Vranić<sup>1</sup>, Andreas Zimmer<sup>2</sup>

<sup>1</sup> University of Sarajevo, Faculty of Pharmacy, Department of Pharmaceutical Technology, Sarajevo, Bosnia and Herzegovina

<sup>2</sup> University of Graz, Institute of Pharmaceutical Sciences, Department of Pharmaceutical Technology and Biopharmacy, Graz, Austria



Endogenously expressed microRNAs (miRNAs) act as post-transcriptional regulators of gene expression in various (patho)physiological processes. miRNA dysregulation is frequently linked to the onset and progression of numerous diseases, hence miRNA-based therapy could be an effective strategy for treating or preventing genetic, immune, or metabolic disorders. Even though miR-27a has been identified as a promising candidate for miRNA mimic therapy of obesity, its use is restricted due to enzymatic degradation and low membrane permeability [1].

To address these issues, we developed cationic lipid nanoemulsions (CNEs) as non-viral carriers for miR-27a. Miglyol® 812 was chosen as the liquid lipid, stearylamine (SA) as the cationic lipid, and Tween® 80 and Poloxamer 188 as surfactants to achieve dual electrostatic stabilization properties. Droplet size, polydispersity index, surface charge, viscosity, and pH value were determined as physicochemical parameters of CNEs. Furthermore, we studied how different mass ratios of CNE and miR-27a, as well as dilution in different media, affect the physicochemical features of the produced complex.

The CNE/miR-27a complex (5:1) was found to be the leading formulation after physicochemical characterization, stability, and cytotoxicity studies. The results revealed that reducing the SA concentration and maintaining the optimal droplet size are essential for the safety and efficacy of the formulations.

#### References

1. Nam, H.Y, et al. Arch Pharm Res (2009) 32: 639–46.

#### Acknowledgements

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DOI: [10.14232/syrptbrs.2022.15](https://doi.org/10.14232/syrptbrs.2022.15)

### Development and optimisation of a novel free-flowing and compressible co-processed excipient containing mesoporous silica and isomalt for the production of solid dispersions

Ana Baumgartner, Odon Planinšek

University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia



Solid dispersions with mesoporous silicon dioxide as a carrier are a promising way to improve solubility of poorly water-soluble drugs. However, mesoporous silica has poor compression and flow properties and is thus inappropriate for direct compression to produce a final dosage form. Hence, a novel co-processed material was developed consisting of mesoporous silica and a sugar alcohol isomalt acting as a binder that connects small silica particles. Such material has improved flow and compression properties that allow for direct compression into tablets, and at the same time has high enough surface area for impregnation with the active ingredient. High shear granulation with water as granulation liquid was used to produce the material and a Design of Experiment study was conducted to examine the effect of different formulation and process parameters (silica to isomalt ratio, water amount and addition rate, impeller rotation speed) on the observed responses (particle size, flow properties, compression properties, specific surface area). Models obtained after the study provided a thorough insight into factors influencing characteristics of the material, however, not all observed responses gave good models. Based on acquired models, an optimised product was developed showing satisfactory characteristics in terms of particle size, surface area, compressibility and tableability. Ibuprofen was chosen as a model drug to be impregnated into the optimised excipient at different ratios by rotary evaporation. Thermal analysis suggested that at lower ratios, ibuprofen was completely transformed into amorphous and/or nanocrystalline form, which are both associated with improved dissolution.

#### *Acknowledgements*

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### **Ternary systems of terbinafine hydrochloride inclusion complexes: preparation, solid-state characterization, dissolution studies**

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Cyclodextrins (CDs) are cyclic oligosaccharides with the ability to modify the physicochemical characteristics of low-soluble drugs via the formation of inclusion complexes. Applying a third component (e.g., polymers, organic acids) may increase the solubility of the complexes. These are usually produced using an organic solvent-requiring method, but there are environmentally friendly, solvent-free methods, such as co-grinding.

In this study, our aim was to prepare terbinafine hydrochloride (TER) containing ternary cyclodextrin systems via co-grinding technology and evaluate physicochemical properties by several analytical tools. As excipient CD derivative, sulfobutylether- $\beta$ -cyclodextrin (SBEB CD) and two polymers (polyvinylpyrrolidone, PVP; hydroxypropyl methylcellulose, HPMC) were used. Physical mixture (PM) contained TER, SBEB CD, and either PVP or HPMC. Co-ground products were prepared from the same composition by grinding PM until complete amorphization. The solvent evaporated and kneaded products were also prepared from the same composition. Products were compared to the pure drug and a marketed product. Following analytical instruments were used to evaluate solid-state properties: X-ray Powder Diffractometry (XRPD), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM). In vitro dissolution studies were performed in simulated intestinal and gastric mediums. XRPD and DSC measurements showed amorphous properties for almost every product, only kneaded products contained a small amount of crystalline TER. According to SEM images particle size of products and TER was comparable. Dissolution properties of the marketed product and TER were similar, while all the products exhibited a better dissolution rate in simulated mediums with higher solubility in the simulated gastric medium.



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### **The implementation of the QbD concept in the development of lipobeads loaded with gemcitabine: the screening study**

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The purpose of this study was to incorporate gemcitabine (GEM) into a novel nanosystem, namely lipobeads (LB), which are hydrogel nanoparticles (NG) surrounded by a lipid bilayer. The Quality by Design (QbD) concept was used with the aim to identify and investigate the formulation factors and process parameters with the greatest influence on the quality attributes of the LB loaded with GEM (LB-GEM).

The preparation technique of LB-GEM included two steps: i) the preparation process of NG encapsulated with GEM (NG-GEM) via a free radical precipitation/dispersion polymerization technique; ii) the preparation process of LB-GEM via the thin film hydration technique, where the NG-GEM dispersion served as hydration medium.

Based on a literature review, six factors were identified as potential critical on the critical quality attributes (CQAs) (size, polydispersity index (Pdl), zeta potential, encapsulated drug concentration and encapsulation efficiency (EE%)) of both the NG-GEM and LB-GEM, and were studied in a screening experimental design with 19 experiments. In the LB-GEM, the encapsulated drug concentration varied between 0.062 and 0.52 mg/ml, while the EE% varied between 7.11 and 52%; these responses being influenced exclusively by the concentration of the monomer. The size (between 36.31 and 387.16 nm) and Pdl (between 0.088 and 0.667) for both NG-GEM and LB-GEM varied significantly with the concentration of the monomer, crosslinker and surfactant.

In conclusion, GEM can be successfully incorporated into LB, and an optimization process will be carried out with the aim to obtain an optimal formulation that meets the quality target profile.



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### **Spray-dried indomethacin-loaded polymeric micelles for the improvement of peroral bioavailability**

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Spray-dried nanoparticle formulations are useful for the development of solid products with a number of advantages. They can be used to develop orally administered, innovative capsules, tablets or water-dispersible powders by providing the appropriate powder rheological properties of the spray-dried product. The increased water solubility due to the more hydrophilic characteristic is especially important in increasing the bioavailability of non-steroidal anti-inflammatory drugs, such as indomethacin, in order to achieve rapid drug release and increased permeability in addition to the possibility of dose reduction.

The morphology of the product was characterized by size analysis based on scanning electron microscopy, laser diffraction and dynamic light scattering. The compressibility and flowability was examined with a stampfvolumeter. During the characterization of the physicochemical properties, the polarity and the encapsulation efficiency were determined, and the drug distribution was examined by Raman spectroscopy. In vitro drug release study was performed in fasting and fed state conditions and an ex vivo permeability study was conducted on porcine intestine.

The product is spherical, suitable for encapsulation, tableting and it contains nano-sized polymeric micelles with monodisperse distribution. Increased polarity and high encapsulation efficiency contributed to the improvement of water solubility, thereby enhancement in in vitro drug release. The active substance distribution of the compressed product is homogenous. Based on ex vivo measurements, the carrier system can be characterized by increased flux and permeability.

Overall, the spray-dried nanoformulation is suitable for increasing the bioavailability of the drug through oral administration.

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### Electrospinning as a novel method for drying iron-oxide-based magnetic nanoparticle dispersions

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Iron-oxide-based magnetic nanoparticles (MNPs) have shown numerous advantages for application in biomedicine, especially as novel drug delivery systems [1]. However, their long-term physical stability in dispersions still represents a big technological challenge. Several methods for the transformation of MNP dispersions into dry products have been thus developed in the last two decades aiming to improve their stability [2]. The methods currently available for drying of MNP dispersions usually require relatively high amounts of excipients to preserve MNP size and result in powdered products, which can provoke adverse health effects in humans, if unintentionally inhaled [3].

The aim of our work was therefore to establish a new method for drying of MNP dispersions, which will give a non-powdered product. Electrospinning was thus employed for drying of MNP dispersions and enabled the preparation of dry product, namely hydrophilic nanofibers loaded with up to 50 % (w/w) of MNPs. The obtained dried electrospun product was rapidly and easily reconstituted in 0.9 % (w/v) NaCl solution without the use of sonication. The polymers used improved also the MNP stability in presence of salts, thus, average hydrodynamic particle size was preserved in a dispersion. The results proved the applicability of the electrospinning method in the formulation of dry non-powdered MNP products, which could be transformed into stable MNP dispersions just before administration.

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### Topical delivery of curcumin-loaded transfersomes gel ameliorated rheumatoid arthritis by inhibiting NF- $\kappa$ B pathway

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**Aim:** To fabricate and evaluate curcumin-loaded transfersomes (Cur-TF) for the targeted delivery and enhanced therapeutic efficacy of curcumin for the treatment of rheumatoid arthritis (RA).

**Methods:** Modified thin-film hydration method was used to prepare Cur-TF which were then embedded into carbopol- 934 gel. They were further evaluated through in vitro techniques for their physico-chemical techniques and in an in vivo in arthritis model for their pharmacological activities.

**Results:** Cur-TF had optimal particle size, spherical morphology, high encapsulation efficiency and sustained drug release profiles. The Cur-TF gel had better in vitro skin penetration than plain curcumin. In vivo findings demonstrated improved clinical, histological and x-ray scores and reduced pro-inflammatory cytokines through NF- $\kappa$ B inhibition.

**Conclusion:** Cur-TF gel delivered curcumin to the arthritic dermal tissue through a topical route and demonstrated promising therapeutic efficacy by significantly alleviating complete Freund's adjuvant (CFA)-induced arthritis.



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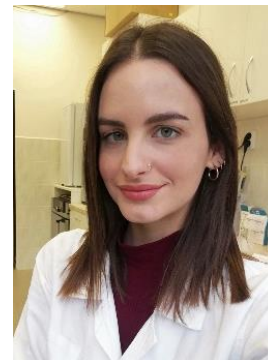
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### Solubility and skin permeability of imiquimod in liposome-dendrimer systems

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Imiquimod (IMQ) is a topically applied imidazoquinoline used for the treatment of several skin diseases, like actinic keratosis and basal cell carcinoma. Traditional formulations deliver only 2% of the applied IMQ because of the drug's poor solubility (<0.002 mg/ml) and low cutaneous permeability. [1] Dendrimers, a new class of polymers, have proved their efficacy in improving the solubility of poorly soluble drugs. [2] The aim of this work was to investigate the effect of a new type of dendrimers on the solubility and skin permeability of IMQ. Different concentrations and generations (G0, G1, G2, and G3) of dendrimers were tested for their effect on IMQ's solubility. The effect of dendrimers was evidenced as their use resulted in a  $4 \times 10^3$  fold increase in the drug's solubility. The optimal preparations were later combined with liposomes and the skin profile of the formulations (with or without liposomes) was examined. G0 with a  $S_{IMQ} \sim 7.5$  mg/ml provided a 10 times higher amount of IMQ to the human epidermis ex vivo than the commercial product, which contains more than 6 times higher IMQ concentration. The addition of liposomes resulted in a lower amount in the epidermis probably due to the lower concentration in the purified liposomes. In conclusion, the findings of this study indicate that dendrimers can increase IMQ's solubility and may be a promising alternative for its topical administration.

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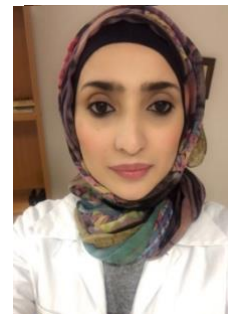
### **Lomustine and *n*-propyl gallate co-encapsulated liposomes for targeting glioblastoma multiforme via intranasal route: *ex vivo* permeability and *in vitro* cell line study**

**Fakhara Sabir<sup>1</sup>, Gábor Katona<sup>1</sup>, Zsuzsanna Schelz<sup>2</sup>, Bence Sipos<sup>1</sup>, Muhammad Naveed<sup>3</sup>, István Zupkó<sup>2</sup>, Ildikó Csóka<sup>1</sup>**

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The study aimed to develop the *n*-propylgallate (PG) and lomustine (LOM)-loaded liposomes suitable for nose to brain delivery for targeting the glioblastoma multiforme. Lomustine is a chemotherapeutic compound that may increase the anti-proliferative effect when applied with PG. Nose to brain delivery of LOM may reduce its toxicity issues in systemic circulation via other invasive routes. The characterization including encapsulation efficiency, loading capacity, *in vitro* drug release and *ex-vivo* permeation studies, were performed. The MTT assay was also directed to assess the anti-proliferative effects of LOM-loaded formulations. Additionally, the IC<sub>50</sub> values representing the anti-proliferative effects of PG and LOM encapsulated liposomes were analyzed. We also studied the cellular uptake by loading liposomes with propidium iodide (PI) and fluorescein isothiocyanate (FITC) fluorescent dye. The particle size of the fabricated liposomal formulations was less than 175 nm with homogenous distribution and negative surface charge (ranging from -36.7±5.0 mV to -28±6.0 mV). The liposomes co-encapsulated with PG and LOM showed anti-proliferative effects on U87 (glioblastoma) and A2780 (ovarian cancer) and NIH/3T3 (murine embryonic fibroblast) cell lines within the investigated concentrations. Our study evaluation suggested the application of this novel combination comprises of PG and LOM nano-formulations as a favorable approach for glioblastoma targeting via intranasal route. Fluorescent microscopic study of PI and FITC-loaded liposomes revealed cellular uptake process was strongly time dependent.

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### Formulation and investigation of the effect of polymers on dermal foam properties using the QbD approach

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Dermal foams are promising drug delivery systems due to their advantages and ease of application. In particular, they are beneficial for the treatment of skin conditions where patients have highly inflamed, swollen, infected and sensitive skin, as the application of the foam minimizes the need for skin contact [1].

My research aimed to develop stable foam formulations containing different types of polymers, to determine the proper methods to investigate their physicochemical and structural properties, and to compare the results of different methods. To ensure quality-based development, the QbD approach was applied. With initial risk assessment, the critical material attributes (CMAs) and the critical process parameters (CPPs) were identified to ensure the required critical quality attributes (CQAs).

The testing methods include the study of foam expansion, foam stability, foam density, foam structure by macroscopic, microscopic, rheological and texture analyzing methods. Through the determination of macroscopic properties, information on the stability of foam formulations can be acquired. With a light microscope, the stability of foams, as well as the kinetics of the destabilization mechanism was analyzed. Rheological measurements could detect deformations in the structure of the foam due to different forces. The dermal application of foam could be modeled with a texture analyzer.

Based on the results, the methods reinforced each other and can be used in preformulation studies to select the optimal formulation.

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### **In vitro quantitative comparison study of insulin SLNs and PLGA NPs as potential carriers for the brain delivery of intranasal insulin**

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



The brain disorders complexity, and high costs of drug development process stand behind the absence of satisfying anti-neurodegenerative therapies. Brain-targeting intranasally-applied nanoparticles represent an optimal way to deliver these therapies as it guarantees the direct transport of the APIs to the brain (N2B). The brain insulin dysfunction has pertained to cognitive processes as insulin constitutes a neuroendocrine link between metabolism and cognition. Solid-lipid nanoparticles (SLNs) and polylactic-co-glycolic acid nanoparticles (PLGA NPs) represent two possible candidates for the N2B of insulin. Four types of Nanoparticles SLNs, PLGA NPs, chitosan-coated SLNs, and PLGA NPs were formulated, then, an in-vitro comparison to the native insulin took place. The physicochemical assessments demonstrated insulin stability in the nanoparticles. The in-vitro experiments showed the superiority of SLNs regarding the dissolution, mucoadhesion, and permeation behaviors over PLGA NPs with a further enhancement by the chitosan-coating. The in-vitro cell line investigations revealed the nanoparticles' safety for the intranasal application and confirmed the in-vitro experiments regarding the nasal mucosa permeation, but not the BBB permeation, because the native insulin is transported actively. In conclusion, an optimal N2B insulin formulation should combine native insulin and insulin-SLNs as the former obtains the immediate effect while the latter ensures effective brain pharmacokinetics.

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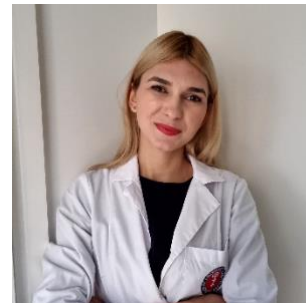
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### Stability studies of cefuroxime loaded self-emulsifying drug delivery systems for ocular administration

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Self-emulsifying drug delivery systems (SEDDS) are water-free dosage forms consisting of an isotropic mixture of oils and surfactants. Following dilution with the aqueous media (lacrimal fluid) with gentle agitation (as occurs with blinking) a fine oil-in-water emulsion is created at the site of administration. The main objective of current project is focusing on developing ocular self-microemulsifying suspensions as a novel approach to improve the stability of administering water-sensitive cefuroxime sodium (CEF). The content assay was performed to determine the potential drug decomposition over time.

SEDDS carriers were obtained by dissolving benzalkonium chloride (0,01% w/w), Cremophor EL, Span 80 and Tween 20 in Miglyol oil (5% w/w) with subsequent CEF (5% w/w) incorporation. The self-emulsification efficiency upon dilution with deionized water was reviewed. The formulations were exposed to 6-months long stability testing. Physicochemical parameters: particle size, pH, Zeta potential were studied and HPLC assay was performed.

The SEDDS suspensions diluted with water were reported to spontaneously form fine emulsions exhibiting an immediate dissolution of cefuroxime. The samples showed negative zeta potential range of -40mV - -50 mV and the mean droplet size from 20  $\mu\text{m}$  to 30  $\mu\text{m}$ . The developed formulations proved to be chemically stable over storage and seem feasible to serve as the effective carriers for water-sensitive drugs.

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### Stability and permeability properties of sodium alginate buccal films

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Idikó Bácskay<sup>2</sup>, Katalin Kristó<sup>1</sup>

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In the pharmaceutical industry the classic drug discovery has lower priority, the companies try to find new and innovative drug administration routes to deliver the API. The buccal mucosa is considered an innovative route which has a lot of advantages. It can be achieved very fast effect locally and systemic equally. In our work we tried to target this administration route with formulating mucoadhesive polymer films. Our aims were investigating the stability and permeability of the formulated films.

The polymer films were prepared in room temperature by solvent casting method. To formulate the films sodium alginate (SA) and HPMC were used as film-forming agent and cetirizine dihydrochloride (CTZ) was added as API to the system. The stability of films was studied with accelerated stability test ( $40\text{ °C} \pm 2\text{ °C}$ ,  $75\% \text{ RH} \pm 5\% \text{ RH}$ ). During the stability test, thickness, tensile strength (hardness), in vitro mucoadhesivity of the prepared films were analyzed as physical properties. Furthermore, the interactions were investigated with FT-IR spectroscopy and the changes in the amount of API were also followed by dissolution study. Cell line permeability study was carried out on TR 146 buccal cells.

Cell line studies show that the permeability of films was enhanced by the presence of citric acid as it increased the total transported CTZ amount, but it was observed that it slightly reduced the stability of the films and all physical parameters that did not affect applicability. In our work we have successfully formulated CTZ-containing buccal films with adequate stability and appropriate absorption across buccal cell line.



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### **Design of ligand anchored polymeric nanoparticles for potential targeted drug delivery in intestinal inflammation**

**Mahira Zeeshan, Hussain Ali**

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Ulcerative colitis (UC) is characterized as inflamed intestinal mucosa of gastrointestinal tract, particularly affecting colon and rectum. It is one of the most common types of inflammatory bowel disease (IBD). Inflammation of intestine led to various pathophysiological events and recruited immune cells including T-cells and macrophages to the inflamed site. Both naïve and recruited macrophages expressed various surface receptors that can be exploited for targeted drug delivery in UC. Considering this fact, ligand conjugated polymeric nanoparticles, galactose-PLGA (GAL-PLGA NPs), were developed that specifically target macrophage galactose type-lectin-C (MGL-2) receptor. The O/W emulsion-evaporation method was adopted, and several study parameters were optimized using QBD approach and Box-Behnken design. The resulted GAL-PLGA NPs have smaller particle size and good encapsulation efficiency. The physical state characterization (TGA, XRD, FTIR) revealed stability and amorphous state of the nanosystem. In-vitro cell-based evaluation indicated biocompatibility with blood cells, peritoneum derived macrophages and colon cells. Further, GAL-PLGA NPs have significant uptake by murine macrophages and colon cells. In-vivo biodistribution and localization study in the dextran sodium sulfate (DSS) induced colitis model confirmed the potential of GAL-PLGA NPs to accumulate at the inflamed intestine. Thus, the ligand based nano-formulation have improved properties to target intestinal macrophages and to reside at the inflamed site for prolonged time for sustained drug efficacy [1].

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### Mannosylated chitosan-based pulmonary drug delivery system for targeting macrophages

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As the causative agent of Tuberculosis resides in the alveolar macrophages, hence an effective drug delivery approach is required for the treatment [1,2]. Therefore, the pulmonary route of drug delivery was exploited by using nanotechnology [3]. Nano dry powder inhaler (nano DPI) was fabricated by spray-drying using mannosylated chitosan (MC) and hyaluronic acid (HA). The polymers were chosen because of their affinity for the surface receptors of macrophages [4]. The confocal imaging demonstrated promising uptake of the nanoparticles by the macrophages. Moreover, cytotoxicity studies revealed no toxic effect of the nanopowder on the A549 cells, RAW 264.7 cells, and the primary culture of macrophages. Furthermore, the nanopowder was found to be compatible with RBCs as demonstrated by the hemolysis study. The human macrophage phenotype analysis was also conducted to determine T-cell activation. Also, the immune regulation study was performed by (2,3-Indoleamine dioxygenase) IDO assay. Altogether, the nano DPI was found to be a promising vehicle for targeting macrophages.

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### Can we turn *Arctostaphylos uva-ursi* L. tea factory waste into herbal extracts for pharmaceutical formulations?

Mirjana Sulejmanović, Senka Vidović, Naffati Abdulhakim, Nataša Nastić, Aleksandra Gavarić

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Increased production of herbal tea generates increased amount of waste derived as an abundant residue that remains after plants processing, specifically herbal dust (up to 40% of the total processed raw material). According to our previous studies, highly useful compounds such as polyphenols, aromatic compounds, chlorophylls, and carotenoids have been recovered from different herbal dusts. *Arctostaphylos uva-ursi* L., commonly known as uva ursi or bearberry, have been traditionally used as a diuretic and antiseptic due to its rich arbutin content.

New technologies considering industrial ecology concepts have pointed out the need for waste recycling, and recovery of resources as valuable compounds as a main research topic. The objective of this research was to consider the impact of conventional solid-liquid (SLE), subcritical water (SWE) and ultrasound-assisted (UAE) extractions on the composition of individual bioactive compounds of *A. uva-ursi* herbal dust. Different extraction conditions were varied during the process. Qualitative and quantitative analysis of bioactive compounds from the *A. uva-ursi* herbal dust extracts was performed using HPLC-DAD.

The major phenolic compounds in *A. uva-ursi* herbal dust determined at different extraction conditions were hyperoside, followed by gallic acid and arbutin. High concentration of arbutin and gallic acid in *A. uva-ursi* extracts obtained by SWE make a great advantage of this green extraction technique over the others investigated. In summary, the conducted study has revealed promising results which showed the possible pathways for further application of green extraction techniques in efficient turn of herbal tea factory waste into functional ingredients for pharmaceutical applications.



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### The effects of chemical permeation enhancer glycols on the skin

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The skin ensures an attractive alternative administration route to conventional drug formulations. However, the stratum corneum (SC), the outermost layer of the skin, forms a barrier against skin permeation. Chemical permeation enhancers are widely used compounds to overcome the barrier function of the skin. They influence the SC structure, which may enhance the dermal drug permeation.

During this research work, we examined three glycols to define their effects on the SC structure and to associate these effects to their permeation enhancer properties. We used NMR spectroscopy to characterize the molecular mobility of SC compounds, and Raman spectroscopy to examine the permeation of a model drug into the different skin layers.

The results from NMR measurements showed that the glycols increased the mobility of SC lipid components, and they also had effects on the keratin filaments. Furthermore, a saturation level for all glycols could be seen, after which the addition of chemicals did not increase the mobility of SC components. The results of Raman spectroscopy showed a significant permeation enhancer effect using the glycols in the formulations, thereby the molecular and the permeation enhancer effect of the examined glycols correlated well during the research.

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### Nanofibers with probiotics combination for treatment of periodontal disease

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Dysbiosis in the periodontal pocket represents the most detrimental factor in the development of periodontal disease [1]. Local administration of probiotic bacterial strains, especially autochthonous oral strains, into the periodontal region has shown to be a promising treatment option. Currently, there is a lack of appropriate systems for precise local delivery of probiotics into the periodontal pocket and thus, nanofibers present an excellent candidate [2,3]. Our work aims to develop nanofibers as a delivery system for a combination of two autochthonous oral bacterial strains.

We developed electrospun polyethylene oxide (PEO) and PEO-alginate nanofibers with incorporated individual probiotic strains and their combination. The probiotic *Bacillus* strains were isolated from a healthy oral cavity. Preservation of bacterial viability is crucial and was addressed by induction of bacterial sporulation prior to nanofiber fabrication. This strategy enabled high spore loading (> 7 logCFU/mg) with no significant decrease of bacterial viability. The resulting nanofiber mats released viable spores in a sustained manner and PEO-alginate nanofibers exhibited a markedly slower release profile than PEO nanofibers.

The developed nanofibers with a combination of two potential probiotics showed the promising characteristics and will be further characterized based on their potential to inhibit the growth of pathogenic bacteria and elucidate the potential synergistic action of the two strains in combination.

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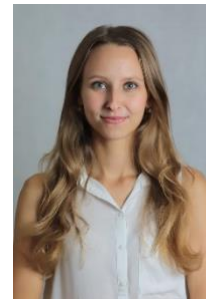
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### Preparation and investigation of meloxicam potassium containing cyclodextrin nanoparticles intended for nasal application

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Nasal delivery of different active pharmaceutical ingredients (APIs) may provide a non-invasive, painless way to treat not just local pathological conditions but to induce systemic or central nervous system effects. However, the selection of appropriate excipients is essential for satisfying nasal absorption of the APIs. For example, mucoadhesive hydrophilic polymers can increase the contact time of the drug with the nasal mucosa, and cyclodextrins may enhance the permeation of the APIs resulting in higher bioavailability.

The aim of our work was to prepare nasally applicable nanospheres containing meloxicam potassium (MELP) – a non-steroidal anti-inflammatory drug – by spray drying using 2 types of cyclodextrins (hydroxypropyl- $\beta$ -cyclodextrin,  $\alpha$ -cyclodextrin) and polymers (hyaluronic acid, poly(vinylalcohol)) as excipients. Physico-chemical characterization, mucoadhesivity test, *in vitro* and *ex vivo* biopharmaceutical investigations were carried out.

Mucoadhesive, spherical nanoparticles containing amorphous MELP were successfully prepared and the formation of API-cyclodextrin complexes were confirmed by thermoanalytical and Fourier-transform infrared spectroscopic measurements. Based on the results of *in vitro* and *ex vivo* permeation studies, the highest amount of MELP diffused from the  $\alpha$ -cyclodextrin based poly(vinylalcohol) containing sample. The prepared formulations may be suitable for delivering MELP to the systemic circulation through the nasal route and relieve pain rapidly after further optimization.

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### **Formulation and investigation of ibuprofen containing inhalable nanocrystals to treat cystic fibrosis**

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Cystic fibrosis (CF) is a lethal genetic disorder, which shows severe lung symptoms. The non-steroidal anti-inflammatory ibuprofen (IBU) slows the disease progression and is well tolerated. Inhalable IBU nanocrystals are advantageous for targeted pulmonary delivery, although IBU is poorly water-soluble and has a low melting point.

We aimed to produce a carrier-free dry powder inhaler containing IBU. We combined high-performance ultra-sonication and nano spray-drying. We expected improved dissolution and proper aerodynamic behavior to provide local treatment for CF.

IBU was solved in ethyl acetate, then sonicated into a polyvinyl alcohol solution. Powders were formulated via spray-drying. The following measurements were executed: dynamic light scattering, scanning electron microscopy, X-ray powder diffraction, in vitro dissolution and in vitro aerodynamic assessment (Andersen Cascade Impactor).

The particle size of the IBU was decreased into the nano range. The diameter of the spray-dried powder was between 500-700 nm and they showed spherical morphology. The dissolution was rapid. The particles gave high lung deposition and had aerodynamic diameters between 2-4  $\mu\text{m}$ , which target the related lung area.

We managed to moderate the difficulties of the IBU during preparation and improve the water solubility. The proper particle size, shape, and dissolution profile besides the outstanding aerodynamic behavior could provide an innovative treatment.

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### Optimization of layering technique and the secondary structure analysis during formulation of nanoparticles containing lysozyme by Quality by Design approach

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Peptides and proteins modifications and formulation of their delivery systems are challenging tasks and hide several risks. For the purpose of this research, we carried out a Quality by Design (QbD) based protein formulation design which can be a key to develop more stable agents with efficient delivery to the target site. The effective delivery of proteins with antimicrobial activity was accomplished through the example of lysozyme (LYZ) in a novel formulation strategy as layer-by-layer polyelectrolyte core-shell nanoparticle [1]. We performed pre-formulation experiments by varying factors such as the concentration of the alginate, mixing time and the pH by the factorial design method. Based on these variations, different formulations of the LYZ were prepared, tested and optimised and the resulting nanoparticles were comprehensively characterised. Furthermore, analytical measurements and assessments were carried out using the different values for the alginate concentration, mixing time and pH which served as determinant factors for the particle size and secondary structure of the LYZ nanoparticle [2].

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### **Analytical Quality by Design (AQbD) approach to the development of in vitro release test for topical hydrogel**

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The aim of our study was to adapt the Analytical Quality by Design (AQbD) approach to design an effective in vitro release test method development using USP Apparatus IV with semi-solid adapter (SSA) for diclofenac sodium hydrogel.

The analytical target profile (ATP) of the in vitro release test and, in addition, ultra high-performance liquid chromatography were defined and the critical method attributes (CMAs) (min. 70% of the drug should be released during the test, 6 time points should be obtained in the linear portion of the drug release profile and the relative standard deviation of the released drug should be not over 10 %) were selected. An initial risk assessment was carried out, in which the CMAs (ionic strength, pH of the media, membrane type, rate of flow, volume of the semi-solid adapter (sample amount), individual flow rate of cells, drug concentration %, and the composition of the product) were identified.

Based on the results, it was possible to determine the high-risk parameters of the in vitro drug release studies performed with USP Apparatus IV with SSA, which were the pH of the medium and the sample weight of the product. Focusing on these parameters, we developed a test protocol for our hydrogel system.



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### Comparison of two commonly used compression analyses for in-die and out of die performance

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The deformation behavior of materials is investigated by using compression analyses. A wide range of different equations can be applied to describe the compression behavior of materials. Heckel analysis is one of the most commonly used compression analyses to characterize the compressibility of a material [1]. In this study, Heckel analysis was compared to compressibility analysis [2]. For this purpose, both in-die and out of die methods of the analyses were performed. The compression analyses were carried out for twelve pharmaceutical excipients in order to verify the applicability of both methods for materials with varying properties. The in-die analysis was performed for six compression pressures. Besides the correlation between the in-die and out of die method, the correlation between both analyses was investigated.

Both methods generated comparable results for the in-die and out of die analysis. Since both analyses are intended to characterize the compressibility of the materials, the results should be similar. However, no correlation can be observed between the analytical methods. Compressibility analysis showed a lower sensitivity to the applied compression pressure as well as a wider linear range in the out of die analysis. Using this analysis could be advantageous over the Heckel analysis which is more commonly used. A comparison of both methods with other established methods for characterizing compressibility could allow a more conclusive evaluation.

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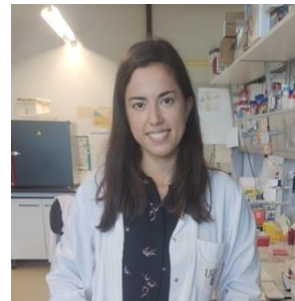
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### Pollen-based microcapsules for pulmonary delivery of anti-tuberculosic drugs

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Lung defense systems and mucociliary clearance pose a challenge to successful pulmonary delivery of antituberculosis drugs. To overcome these barriers, our group has developed pollen-based platforms, taking advantage of their special 3D structure which confers resistance and bioadhesion to mucosal surfaces.

Chamomile (*Matricaria chamomilla*) pollen grains were treated for the obtention of hollow sporopollenin microcapsules (1). Their in vitro distribution profile showed a mass aerodynamic diameter (MMAD) of 8  $\mu\text{m}$  and a fine particle fraction (FPF) of around 30%. Stable and spherical 200 nm blank and 1, 2.5 and 5% rifabutin (RFB) loaded protamine nanocapsules (NCs) were prepared (2), achieving a RFB association of 54, 46 and 42%, respectively. Their diffusion in simulated lung media was progressive with a linear and sustained RFB-release pattern. RFB NCs were microencapsulated into chamomile sporopollenin microcapsules, obtaining an encapsulation efficiency and loading capacity >50%. Aerodynamic distribution showed a MMAD between 10-14  $\mu\text{m}$  and a FPF within 17-24%.

Chamomile pollen microcapsules presented a natural microneedle-like design with a reasonable aerodynamic profile to reach alveolar macrophages. Further, the developed protamine nanocapsules revealed considerable entrapment efficiencies of lipophilic rifabutin and satisfactory physical and biological stability. The developed platform combined the benefits of nanotechnology and the capacity of pollen grains to be anchored to the mucosa for obtaining a multi-step delivery platform. Future studies will be carried out coating pollen grains with excipients to improve flow properties.

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### **Modelling urinary catheters with innovative approaches for patient's using QbD & 3D bioprinting**

**S P Yamini Kanti, Ildikó Csóka, Livia Adalbert, Orsolya Jójárt-Laczkovich**

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Catheters have been widely used over forty years by patients who have been unable to empty their bladders in a natural way is to use Catheters. But, using catheters comes up with many complications such as painful and traumatizing process, causing injuries and can also cause different types of Urinary Tract Infections.

Based on the end -use, the market of catheters is classified as urinary incontinence & spinal cord injuries and based on the type of product, the market is classified into – Disposable and Reusable external catheters. In clinical practice, the occurrence of Bacterial Colonization, Antibiotic Resistance, Kidney and Bladder damage, Septicemia, Urethral trauma and other kinds of urinary Tract Infections have made it necessary to improve the quality and design of the Catheters for the end users.

Such incidents with all the understanding of the critical factors, addressing the expectations and needs of the patient's and users will determine the quality and the cost of the catheters. As Consumers & market behavior has changed during the COVID-19 pandemic, industries will have to restructure their strategies in order to comply with the changing market requirements. Applying new approaches such as Quality by Design and 3 D bioprinting will provide an efficient tool to integrate the driving elements such as quality, cost of the product and needs of the end-user, and hence facilitate the life cycle of product in line with the expectation of Pharmaceutical Industry-Regulatory and Consumer.





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### **Intensification of anthocyanin extraction from *Sambucus nigra* fruits using ultrasonic probe: Effect of factors, and comparison with conventional extraction approach**

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There is a growing interest in the use of plant raw materials raised by evidence concerning their potential as a reputable source of new biologically important molecules and as a high-quality dietary supplement ingredient. Elderberry (*Sambucus nigra* L.) fruit has great industrial potential due to its high content of anthocyanins – primarily cyanidin-3-sambubioside, cyanide-3-O-glucoside, cyanidin 3,5-diglucoside, and flavonoids - mainly quercetin, rutin, quercetin-3-O-glucoside.

Conventional solid-liquid extraction (SLE) is suitable for isolation of these compounds depending on the applied process parameters. The question is whether it is cost-effective concerning extraction time, required amount of solvent, and efficiency. The application of ultrasound-assisted extraction (UAE) using ultrasonic probe can intensify the extraction rate by the rupture of the cell wall due to formation of microcavities with minimal energy loss.

In this study, the effectiveness of SLE and UAE using ultrasonic probe for the isolation of phenolic compounds from dried elderberry fruits was examined. SLE with 30% ethanol was performed for 24h. During the UAE process using the same solvent, extraction time (2-6 min), and sonication amplitude (20-100%) were varied. Changes in temperature, energy consumption, and ultrasonic power were observed.

After measuring the content of total phenols and monomeric anthocyanins, it was determined that UAE has higher efficiency in comparison to SLE. The important advantage of UAE was significantly shorter extraction time. Overall, it appears that UAE using ultrasonic probe can give significant process intensification benefits and effectively be used for the extraction of valuable compounds from plant material.



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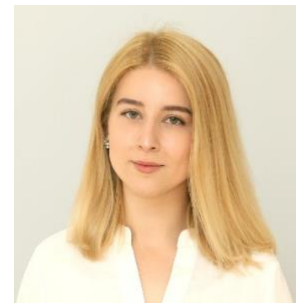
### Casein-coated iron oxidemagnetic nanoparticles–preparation and evaluation for possible application in hyperthermia treatment

Stanislava Simeonova<sup>1</sup>, Tsenka Grancharova<sup>2</sup>, Plamen Zagorchev<sup>2,3</sup>, Bissera Pilicheva<sup>1, 3</sup>

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Magnetic iron oxide nanoparticles have been thoroughly investigated for a wide variety of applications, including diagnostics and therapeutics. The aim of this study was to develop casein-coated iron oxide nanoparticles with optimized characteristics for further application in hyperthermia therapy. Three models of bare magnetic nanoparticles were developed at varied operating conditions such as temperature, stirring speed and reagent addition sequence during the synthesis. The obtained bare nanoparticles were analyzed for particle size and size distribution, and for their tendency for aggregation. The magnetic properties were confirmed by magnetic separation of the solid phase from the resulting suspension using a permanent magnet. Based on the results, optimized process parameters were outlined for further research.

For casein coating, impregnation of casein micelles with iron salts with subsequent precipitation was applied. For the characterization of the obtained casein-coated iron oxide nanoparticles scanning electron microscopy, transmission electron microscopy, dynamic light scattering, and infrared spectroscopy were used. Nanoparticles were in the range around 10-60 nm, revealing nonuniform size distribution, tendency for aggregation and uneven protein coating. Further optimizations of the coating procedure are needed to obtain satisfactory wrapping of the magnetic cores regarding their physical stability.



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### Synthesis and investigation of a mucoadhesive chitosan derivative for intranasal drug delivery

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Chitosan is in the focus of scientific interest due to its remarkable properties such as biodegradability and mucoadhesiveness among others. Its amino group content is mainly responsible for the mucoadhesivity as a result of the positive charge after protonation. Covalent modification of amino groups of chitosan with L-cysteine can result in further mucoadhesiveness improvement because the total number of amino groups will not change after the reaction and the thiol groups of L-cysteine might result in stronger interaction with nasal mucosa. In this work, our aim was to synthesize chitosan-cysteine conjugate containing moderately high amount of L-cysteine. Further aim was to determine the thiol content of the derivative, as well as to evaluate its mucoadhesiveness under nasal conditions (pH=5.6, 32°C) compared to the starting chitosan by measuring the loss and storage moduli, and the work of adhesion. The characterization of crystallographical and thermoanalytical properties also belonged to our goals. The reaction mixture contained 0.50 g of chitosan 0.70 g of L-cysteine, 1.2 g 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide and 0.32 g of N-hydroxysuccinimide in 50 ml of pH=4.7 2-(N-morpholino)ethanesulfonic acid solution. After 5 h of reaction the polymer was dialyzed multiple times and the product was freeze-dried. The chitosan-cysteine polymer contained moderately high amount of thiol groups. The product showed amorphous nature, moreover DSC and TG thermograms indicated different entity from the starting polymer. The adhesion work of the derivative was significantly higher ( $p < 0.001$ ) in comparison to starting chitosan. The chitosan derivative seems to be highly mucoadhesive in nasal conditions, however additional measurements are required to confirm the feasibility of this material in nasal formulations.

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### Derivation of appropriate parameters for photothermal therapy, mediated by iron oxide nanoparticles

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Generally, the photothermal therapy involves radiation in the near-infrared region coupled with a photo-absorbing agent to convert laser energy into heat, inducing thermal damage. This type of therapy can lead to a tumor specific treatment with minimal damage to surrounding healthy tissues. Assuming the potential effects of various parameters such as laser wavelength, power density, duration of laser irradiation, penetration depth and concentration of the photo-absorbing agent, is essential to determine the right dose of energy that is necessary to produce hyperthermia.

In our study, we aimed at measuring the light penetration of 810 nm diode laser in tissues and evaluate the efficiency of iron oxide nanoparticles as near-infrared light absorbents. Iron oxide nanoparticles were prepared by co-precipitation technique. Different nanoparticle concentrations and porcine muscle tissues of varied thickness were used to derive the optimum parameters for further photothermal therapy. It was found that at a power density of 0.33 W/cm<sup>2</sup>, which is the skin threshold limit for 810 nm laser irradiation, the effective depth of beam penetration, at which hyperthermia would be achieved, is 3 mm.



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### Development and characterization of lysozyme loaded gum arabic as innovative oral films

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Up to date, the administration of a biological macromolecular drug by a route other than the traditional invasive one represents a challenging goal [1]. Buccal films represent an innovative carrier system with well-established advantages. The present study aimed to develop lysozyme-loaded gum arabic (GA) films and evaluate their suitability for both the buccal application and coating process. The loaded-films were produced by solvent casting method according to 2<sup>3</sup> full factorial design; propylene glycol (PG), citric acid (CA), and GA quantities were used as investigated factors while the biological activity, tensile strength, mucoadhesivity, and other physical properties were applied as the responses. In addition, the investigation of minimum film forming temperature (MFFT) and thermal behavior, Raman mapping, and FT-IR measurements were also performed. GA demonstrated a conformation stabilizing property; therefore, the obtained films demonstrate a considerably high biological activity, which agrees with the literature. The samples present excellent mucoadhesive property and tensile strength with an obvious elasticity, considerable thermal stability and low value of MFFT. The samples elicit high water-absorbing capacity and short disintegration time which is associated with an initial burst release followed by an extended-release step. It could be concluded that GA represents an innovative carrier system for biopharmaceuticals with novel properties such as pronounced mucoadhesivity and stabilizing property for developing either oral mucoadhesive films or as subcoating/coating process.

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### Risk-based optimization of liposome-based nano-carrier systems

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The number of requirements for pharmaceuticals is growing dynamically; thus, conscious design and analysis is needed to incorporate these needs into development plans. It can be ensured by a risk assessment-based approach as part of the Quality by Design method [1]. Liposomal formulations are innovative forms of drug delivery systems; however, their development is a challenging process. Certain factors decisively influence the vesicles, while the relevant properties of the product vary depending on the development goals. Different production methods require different material characteristics and production settings. Identifying the product profile of the formulation, the critical quality attributes of the liposomes, and the manufacturing parameters that have a critical effect on the result will help in the development process. This work determined the requirements of liposomal formulations prepared by the thin-film hydration method and the factors influencing the final product. The formulations were optimized for vesicle size, size distribution, and surface charge, and the relationships describing the results obtained by changing the production settings were investigated [2]. The tested critical factors included the type, amount, and ratio of the wall-forming agents, the hydration medium and cryoprotectant, the working temperature, and additional physical parameters of the production technique. After determining the appropriate manufacturing conditions, the surface charge of the formulations was optimized by adding dicetylphosphate or stearylamine to the formulations following a factorial design. Liposomes have been characterized via morphological, thermodynamical, and structural studies.

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#### Acknowledgements

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# **Abstracts**

## ***Flash presentations***





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DOI: [10.14232/syrptbrs.2022.46](https://doi.org/10.14232/syrptbrs.2022.46)

### Effect of Process Conditions and Parameters on Low-Dose Drug Uniformity Formulated as Pellets

Azza A.K. Mahmoud, Yousif H-E.Y. Ibrahim, Géza Regdon jr., Katalin Kristó

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Multiparticulate delivery systems (MPDSs) such as pellets are well-known advantageous over the other conventional solid dosage forms such as tablets, regarding the dose accuracy and delivery effectiveness. The extrusion and spheronization technique represents the highly recommended method regarding the loading capacity and possibility to acquire the required properties such as roundness and content uniformity [1]. Drugs with low doses may encounter uneven distribution within the whole powdered mixture to be processed; accordingly, mixing steps in both dried form and wetted conditions should carefully be evaluated. Moreover, the environmental condition during the production should be carefully monitored [2]. The aim of the study is to investigate the effect of material attributes such as particle size, crystallinity, and deformability on prepared pellet quality. The other goal is to study the effect of the homogenization mixing process parameters on the content uniformity (in both dried and wetted systems). Also, the process parameters of the wet-kneading in the high shear granulator will be thoroughly monitored by applying a specially designed chamber supplied with sensors having the ability to precisely and continuously measure the distribution of the pressure, temperature, and relative humidity (RH). Furthermore, a full factorial design with a center point will be adopted to study the effect of the various critical process parameters and material characteristics on the quality of the targeted pellets.

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### Design and optimization of dexamethasone containing *in situ* gelling mucoadhesive eye drops

Boglárika Szalai, Mária Budai-Szűcs, Orsolya Jójárt-Laczkovich

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



Eye drops are commonly used for the treatment of ocular diseases. The complex elimination mechanisms of the eye cause poor bioavailability of this route of administration. Dexamethasone is frequently used to treat non-infectious inflammatory ocular diseases. The low water-solubility and penetration ability of dexamethasone decrease its biological effectiveness. My PhD work aims to formulate *in situ* gel-forming mucoadhesive eye drops containing dexamethasone-cyclodextrin inclusion complex to improve the residence time and solubility of the active pharmaceutical ingredient.

During the preformulation studies, optimal cyclodextrin type and concentration were chosen based on the results of phase solubility tests and the stability constants of the complexes.

Poloxamer was used to form thermosensitive *in situ* gelling eye drops. To provide proper mucoadhesivity, two mucoadhesive polymers were combined with it. Rheological studies were carried out in order to investigate the gelation: gelation temperature, gelling time at body temperature and gel strength were measured. Mucoadhesivity of the eye drops were examined with a texture analyzer. A mucin covered surface was used to imitate the surface of the eye. Adhesive force and adhesive work were determined based on the force-distance curve.

The preliminary experiments helped to choose the optimal concentration range of the components to form mucoadhesive *in situ* gelling eye drops. 33 full factorial design was applied to evaluate the effect of the composition on the gelation and the mucoadhesivity.

The purpose of the factorial design is to find the ideal composition and to explore the correlation between the composition and the dissolution.



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### **An investigation into relationship between thin films mechanical and rheological properties**

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Thin films, as polymers-based flexible dosage forms, are versatile platform for drug delivery. Good mechanical properties are prerequisite and therefore must be assessed to ensure targeted film performance. The following work aims to explore the relationship between common mechanical properties and thin film characteristics obtained by oscillatory rheometry.

Thin films were prepared by solvent casting, using different polymers (hypromellose-HPMC, poly(ethylene-oxide)-PEO, sodium-carboxymethyl cellulose-CMC, polyethylene glycol-polyvinylalcohol-graft-copolymer-KIR, sodium-alginate-SA). Young's modulus (YM), as common mechanical parameter, reflects thin films stiffness, and is calculated as the slope of the stress strain curve, obtained using Z-LX Table-Top Testing Machine (Shimadzu, Japan). Viscoelasticity of the investigated samples was evaluated based on the complex modulus ( $G^*$ ) values, determined by oscillatory rheometry (Rheometer Rheolab MC 120, PaarPhysica, Germany).

Cluster analysis performed indicated that thin films containing same film-forming polymer were clustered together, with the exception of KIR. This indicates that polymer type is prevailing factor affecting film stiffness and resistance to deformation. High level of correlation was revealed within each cluster group, as higher YM values were accompanied with higher  $G^*$ . Both YM and  $G^*$  values for KIR-based films showed high variability, ranging from 51 to 281 MPa for YM and 2 to 50 MPa for  $G^*$ , indicating that other factors, apart from polymer type are interfering.

The obtained results indicate that it is possible to predict trend in YM based on  $G^*$  values within the cluster of samples prepared from the same polymer.  $G^*$  parameter is not extensively explored and provides possibility to further explain film inner structure.

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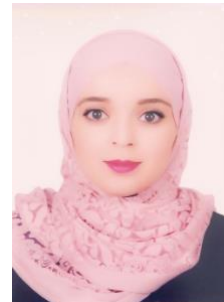
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### Formulation of a combined dry powder inhalation therapy for cystic fibrosis

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Cystic fibrosis (CF) is a common lung disease, caused by a gene mutation (CFTR). It leads to abnormal mucus accumulation, chronic airway infection, inflammation, progressive lung damage and death. Therefore, there is no cure for CF, but a range of treatment can help control symptoms, reduce complications, and improve the quality life of patient. Through the pulmonary administration route, inhalation therapy is widely used for the treatment of local pulmonary disorders. The dry powder inhalers (DPIs) are the most used and stable form of drug administration via lung.

Since the Cystic Fibrosis Foundation recommends mucolytic, antibiotic, and anti-inflammatory agents, in the same sequence for inhaled medications; our project is developing a novel DPI containing a combined therapy of mannitol, levofloxacin and/or ketoprofen by controlled release. The aim of this combination is to achieve the patient convenience with the highest drug effectiveness at the same time.

The combination powder will be produced by spray dryer and under controlled conditions to obtain nanoparticles with same particle size distribution. Laser scattering, FT-IR, XRPD, DSC, SEM and aerodynamic particle size analysis are the investigation methods for the particle characterization. Quality by design (QbD) approach will be used to predict the final quality of the products.

It is expected to design a novel promising inhaled combined therapy for cystic fibrosis with; I. improved aerodynamic properties, II. a high release profile, III. an increased local deposition in the lung cell, and IV. a long-term stability.



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### **An investigation into multiparticulate units printability by selective laser sintering**

Ivana Vasiljević, Jelena Parojčić

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Selective laser sintering (SLS) is a 3D printing process, described as a suitable technology for diverse dosage forms and highly detailed structures fabrication (1). Its application in multiparticulate units (MPU) preparation is scarce. The aim of this work was to assess the printability of MPU using SLS.

The MPU consisted of: model drug (10%): ibuprofen (IBU)/caffeine (CAF); polymer (87%): poly(ethylene)oxide (PEO, Polyox WSRN12K)/ethyl cellulose (ETC, Ethocel)/methacrylic acid-ethyl acrylate copolymer (EUD, Eudragit L100-55); colorant (3%): Candurin® Gold Sheen. "Large" (2 mm) and "small" (1 mm) MPUs were printed using SLS printer Sintratec Kit (Sintratec AG). High granule true density and low particle fines fraction, i.e. high yield, were identified as printability indicators.

It was observed that large MPU exhibited higher true density, as well as higher particle fines concentration, i.e. lower yield in the desired particle size. True density was more affected by the model drug than particle size and CAF-MPU exhibited higher true density (1.21-1.38 g/ml) than IBU samples. ETC-MPU exhibited the lowest true density (1.19-1.22 g/ml) and particle fines fraction (3.6-18.5%), indicating the high yield obtained. EUD-MPU true density was the highest (1.23-1.38 g/ml), due to prominent binding of EUD fine particles. PEO-CAF samples exhibited extremely high particle fines fraction (32.6-48.9%).

SLS printing may be used for MPU preparation. Preliminary data indicated that smaller MPU may be advantageous for further processing into tablets, while larger MPU are challenging to obtain due to relatively low yield.

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### Improvement of dimenhydrinate solubility by complexation with $\beta$ -cyclodextrin

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Dimenhydrinate (DMH) is slightly soluble drug which belongs to class II of Biopharmaceutics classification system (low solubility, high permeability). To improve DMH solubility and enhance its bioavailability inclusion complexes with cyclodextrins (CDs) can be formed. These cyclic oligosaccharides with a hydrophilic outer surface incorporate a drug in the lipophilic central cavity and increase its solubility.

Phase solubility studies, where the change of drug solubility is corresponding to CD concentration, can be conducted to assess the binding characteristics of DMH and  $\beta$ -cyclodextrin ( $\beta$ -CD) and to determine the values of stability constant ( $K_s$ ), complexation efficacy (CE) and utility number ( $U_{CD}$ ). A-type phase solubility isotherms are characteristic for water soluble complexes. Optimal value of  $K_s$  is 100-5000  $M^{-1}$ . Lower values imply very labile complexes with premature drug release and insignificant solubility improvement. Higher values imply very stable complexes with incomplete or obstructed drug release from CD cavity. The value of CE depends only on the slope of phase-solubility profile and it's is less variable compared to  $K_s$  value which depends on the intercept and intrinsic solubility which are affected by excipients used in formulation.

The results of the conducted phase solubility studies showed  $A_L$ -type isotherm. The slope was less than unity which implies that  $\beta$ -CD enhances the solubility of DMH linearly and forms 1:1 complex. The value of  $K_s$  was 171,10  $M^{-1}$  and the CE value was 3,45.  $U_{CD}$  value  $\geq 1$  was achieved in 1,8% solution of  $\beta$ -CD thus solubilization of 25 mg of DMH was adequately provided by complexation with  $\beta$ -CD.





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### Comparison of single-needle and nozzle-free electrospinning methods

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The most common and simplest way to produce nanofibers is electrospinning (ES), a process in which a liquid jet is generated by an electric force and is then transported towards the collector. The easiest way to form nanofibers from electrospinning solution is by single-needle ES, where fibers are formed through a metal nozzle. Since only one jet is formed through the needle at a time, the productivity of single-needle ES is low. In contrast, nozzle-free equipment can increase the productivity and could be used for massively producing nanofibers.

Our aim was to produce rapid-release ciprofloxacin-loaded nanofibers by single-needle ES and then to increase productivity by transporting the method into a nozzle-free ES and finally, to compare the two preparation methods.

For the comparison micrometric properties were examined by scanning electron microscopy (SEM), physicochemical properties by powder X-ray diffraction (XRPD) and differential scanning calorimetry (DSC) and the homogeneity of the nanofibrous mats by Raman mapping. The rate of drug release was determined by *in vitro* dissolution tests.

Based on our results, nozzle-free ES provides acceptable morphology and more homogeneous ciprofloxacin distribution than the traditional single-needle ES technique. From the nanofibrous mats, the drug release was immediate and complete. The ciprofloxacin was in amorphous form in every nanofibrous sample. The nozzle-free ES method may be worth further development in the future.

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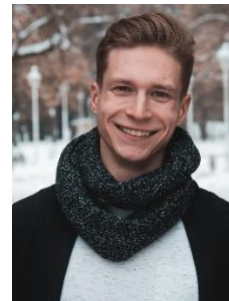
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### **Additive manufacturing in the service of personalized medicines – opportunities and future plans**

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After the expiration of the first patents of various 3D printing technologies, different manufacturers have appeared on the market with desktop 3D printers. Over the last decade additive manufacturing has become a commonly available technology and made its way to most of the industries including the pharmaceutical industry.

Fused Deposition Modeling (FDM), Inkjet – powder bed and Stereolithography (SLA)<sup>1</sup> are the most investigated technologies which offer a promising tool for pharmaceutical technological application. The industrial significance of 3D printing was supported by the FDA approval of the first 3D printed medicine Spritam® (Aprecia Pharmaceuticals)<sup>1</sup> combining the precision of 3D printing and formulation science to produce rapidly disintegrating levetiracetam-containing tablet for oral suspension. Besides the industrial utilization 3D printing can transform healthcare through personalized medicine, thus improving patient compliance by tailoring the medication to the patient. This can be achieved through on-demand manufacturing in clinical settings to offer the best medical care. FabRx Ltd. (UK)<sup>2</sup> applies FDM technology to produce personalized tablets (printlets) based on the physiological parameters of each individual patient. Their development in field of rare diseases, metabolic disorders and nutraceuticals already reached clinical trial phase. Besides pharmaceutical formulations, Additive Manufacturing (AM) also has a huge impact in the medical device industry. The best fit for the given patient in orthopedic implants can be achieved by Digital Imaging and Communications in Medicine (DICOM) processing connected with metal 3D printing.

Based on the mentioned opportunities our aim is to develop a fully customizable FDM based implantable drug delivery system mostly with intranasal application routes.

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### Improving the bioavailability of favipiravir by using human serum albumin nanoparticles

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Favipiravir (FAV) is an antiviral agent that inhibits RNA-dependent RNA polymerase of several RNA viruses such as Ebola virus and now COVID-19. It classified as BCS class IV drug. In this study, a Favipiravir-loaded human serum albumin nanoparticles (FAV-NPs) were prepared to overcome the low solubility and low permeability. The FAV-NPs were prepared by pH-dependent coacervation method with glutaraldehyde (as a crosslinking agent). The FAV-NPs were investigated for both gastrointestinal and nose-to-brain conditions. This method has been optimized based on several factors such as drug:HSA ratio, pH, amount of crosslinker and incubation time of drug-HSA. The prepared FAV-NPs were characterized regarding to particle size, PDI, zeta potential (before and after freeze-drying) and encapsulation efficiency (EE%) (by using a validated HPLC-DAD method). The study showed the optimized formulation was reached by applying 1:1 drug:HSA ratio, pH =  $7.6 \pm 0.1$ , 60  $\mu$ l of glutaraldehyde 8%v/v and 80 min incubation time. The optimized FAV-NPs showed 203 nm particle size with a zeta potential of -34.1 mV and 0.25 of PDI before freeze-drying, whereas 210 nm particle size, -25.9 mV zeta potential and 0.195 of PDI after freeze-drying, respectively. The developed HPLC-DAD method was a sensitive, accurate and precise for determination of FAV. According to this analytical method we found that EE% was 99.72 %.

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### Development of solid self-nanoemulsifying drug delivery systems (s-SNEDDS) for oral delivery of lysozyme

Merima Sirbubalo<sup>1</sup>, Tamás Sovány<sup>2</sup>, Katalin Kristó<sup>2</sup>, Géza Regdon jr<sup>2</sup>, Edina Vranić<sup>1</sup>

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Self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic mixtures of lipid, surfactants, and cosolvents, that instantly produce ultrafine O/W emulsions upon gentle agitation in GI fluids. SNEDDS can be produced in a very simple and cost-effective manner, but these liquid formulations have many drawbacks. Therefore, different solidification techniques (e.g. adsorption to solid carriers), were used to transform liquid SEEDS into solid powders, which can be further processed into other solid dosage forms and thus obtain better physical and chemical stability. SNEEDS have been widely investigated in recent years to improve the oral bioavailability of poorly water-soluble drugs, but it was also reported that these systems can address challenges associated with the oral delivery of protein drugs. Proteins loaded inside the oil droplets of SNEDDS are effectively protected towards proteolytic activity and SEDDS can also exhibit mucus-permeating properties and/or can act as permeation enhancers leading to improved bioavailability [1].

Despite all of the advantages, incorporating proteins in SNEDDS can be very challenging. To be loaded into the SNEDDS, their lipophilicity should be increased first. Among several techniques that have been adopted to increase the lipid solubility of protein drugs, reversible hydrophobic ion pairing (HIP) complexation is the most commonly used and is based on forming ionic interactions between a charged hydrophilic molecule with an oppositely-charged counterion [2]. To the best of our knowledge, no earlier attempts to use s-SNEDDS for lysozyme oral delivery have been made. Thus, the objectives of the present study will be to develop, optimize, and evaluate s-SNEDDS for oral delivery of lysozyme by applying the QbD approach.

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### The influence of SMEDDS composition and the water ratio in granulation dispersion on attributes of granules prepared by wet granulation

Mila Kovačević, Ilija German Ilić, Alenka Zvonar Pobirk

University of Ljubljana, Faculty of Pharmacy, Department of Pharmaceutical Technology, Ljubljana, Slovenia



Self-microemulsifying drug delivery systems (SMEDDS), as formulation strategy developed for solubility improvement of poorly water-soluble drugs, are composed of lipids, (co)surfactants, hydrophilic cosolvents (optional) and drug, that is dissolved within the mixture (1). As such, SMEDDS are liquid dosage forms and therefore require transformation into solids, to achieve higher patient compliance, better stability, lower production cost in comparison to soft gelatine capsule filling (2). Within the present study, wet granulation was used as solidification technology, with SMEDDS water dispersion used as granulation fluid and mesoporous Syloid® 244FP as solid carrier. The purpose was to investigate whether granulation dispersion composition (different lipid/surfactant ratio in SMEDDS and different water dilution ratio) influence granules quality attributes, with special attention given to particle size, flowability, dissolution and self-microemulsifying properties.

Lipid/surfactants ratio in SMEDDS formulation impacted granules particle size in terms of positive correlation with  $d_{50}$  value. Likewise, particle size was affected by water/SMEDDS ratio in granulation dispersion with respect to higher SMEDDS share. Particle size with  $d_{50}$  227-578  $\mu\text{m}$  ensured excellent and good flow properties (Ph. Eur. criteria), despite high SMEDDS content (up to 2.91g SMEDDS/1g carrier) and consequently high drug loading. However, there were no big differences between granules *in vitro* dissolution properties, as the exhibited profiles were similar (81-88% drug released in first 5 minutes), but still faster than pure drug, with all formulations releasing full extent of the drug.

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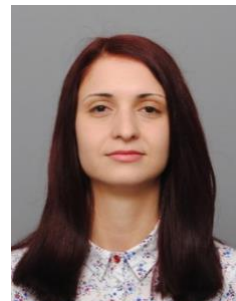
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### Nanocarrier-mediated nose-to-brain drug delivery for Parkinson's disease

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The intranasal route attracts attention due to the specific anatomical and physiological features of the nasal cavity. Intranasally administered drugs can be transported to the central nervous system within minutes due to the connection between the nasal cavity and the brain via olfactory neurons. Nowadays, there are approaches to increase the efficacy of drugs by including them in bioadhesive formulations for nasal administration. The development of nanocarriers (NCs) is promising for improving the brain therapeutic delivery. NCs have some advantages over conventional formulations including encapsulation of one or more drugs, loading of higher doses in a small volume of formulation, controlling drug release, and targeting drugs to diseased locations. The rapid and preferential distribution of drugs to the brain via the intranasal route may lead to the reduction of systemic exposure and peripheral adverse effects.

The purpose of this review is to present various NCs that encapsulate drugs for targeted nose-to-brain delivery for the treatment of neurodegenerative diseases such as Parkinson's disease (PD). Along with the traditionally recognised pathological hallmarks of dopaminergic neuronal death and intracellular  $\alpha$ -synuclein depositions, iron accumulation, elevated oxidative stress and lipid peroxidation damage are further features of PD pathophysiology. Therefore, active substances that can affect the disease by various mechanisms e.g., drugs increasing dopaminergic mediation or neuroprotectants which discontinue the progress of the disease (iron chelators, antioxidants) can promote direct access to the central nervous system by inclusion in nanocarriers. This review highlights the recent advances of nanocarriers in enhancing drug activity for PD therapy.

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### Preparation of functionalized titanate nanotubes to improve toxicological profile and bioavailability

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Nowadays, inorganic nanoparticles have gained enormous attention in numerous fields such as pharmacy, medicine, agriculture, energy, etc. due to their tremendous potentials and novel characteristics offered by their nano size. These multiple applications and unique design make them widely presented around us in daily life therefore almost impossible to avoid.

Nanotubes are one of these nanoparticles that were introduced to the world as novel drug delivery system, and first appeared as carbon nanotubes (CNTs) then titanate ones. Titanate nanotubes (TNTs) were the answer to the previously detected problems of CNTs due to their special characteristics that make them ideal carriers for pharmaceutical applications. Some of these unique properties of nanoparticles were created by altering their surface properties to reduce toxicity [1, 2], achieve targeted delivery, enhance cell internalization or obtain proper bioavailability which was previously done successfully with TNTs using hydrophobic materials such as magnesium stearate or trichlorooctylsilane as a technique to enhance their absorption into the systemic circulation since their hydrophilicity negatively affects their permeability through the GIT [3]. The aim of this study is to functionalize TNTs with PEG, which is suitable to further improve aqueous solubility and reduce toxicity [4]. The results revealed that direct linking of PEG-to TNTs was unsuccessful, therefore, trichloroacetic acid and citric acid were investigated as possible linkers. The impact of functionalization on in vitro/in vivo toxicity, and on tablettability will be investigated. Tablets as final dosage form are planned to be prepared with both conventional compression and 3D printing.

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### Pharmaceutical study of essential oil-loaded liposomal formulations

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Liposomes are lipohydrophilic nanocarriers used in drug delivery and exhibited substantial clinical successes. Essential oils (EO) are lipophilic chemicals with several medical and physiological effects. Studies suggest that not only liposomes are promising carriers for EOs and increase their stability but also EOs have effects on the liposomal structure. There is still a lack of data on this field; thus, the topic requires more attention for better investigation of the possible evaluation (1).

Accordingly, the goal of this work was to study the effects of different kinds and ratios of EOs on liposomal formulations.

Liposomes were made from phosphatidylcholine, cholesterol (60:40 weight ratio), and a diverse range of ratios of EOs (5-200 percentage of the whole lipid mass concentration), using the thin-film hydration preparation method (2). The vesicles were characterized by a zeta-sizer via the dynamic light scattering method. The zeta potential and vesicle size values were investigated, and furthermore, the possible correlation between various EOs with different concentrations was identified in this study.

After adding a certain ratio of EOs to the formulations, those have become polydisperse (higher polydispersity index than 0.3) and bigger than 200 nm size was measured. Zeta potential values tend to be negative, and a correlation between them was detected.

The impact of EOs on liposomal formulation has been shown. These data may be used for liposomal optimization and simultaneously also to increase the bioavailability of EOs.

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### Development of in situ mucoadhesive-thermosensitive gel of amoxicillin for intranasal delivery

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Acute Bacterial Rhinosinusitis (ABRs) is one of the most common upper respiratory tract infections caused by bacteria and infects the lining of the nasal cavity and sinuses. Amoxicillin is recommended as the first-line therapy for the treatment of ABRs. However, oral administration of Amoxicillin can affect systemic circulation and potentially cause some adverse reactions. Moreover, oral administration shows poor bioavailability due to the first-pass metabolism, leading to frequent dosing of therapy. Nasal drug delivery becomes an alternative approach as it allows delivery of the drug directly to the nasal cavity, provides higher drug concentrations locally, and has the potential to minimize systemic adverse effects.

This study aims to develop an intranasal formulation of Amoxicillin by the mucoadhesive thermo-gelling system that could possibly retain the drug in the nasal mucosa for a certain period of time while releasing the drug slowly to obtain optimal drug absorption. Bovine Serum Albumin will be employed as a drug-nanocarrier that might improve the permeability and retention profile of the preparation, as well as Poloxamer 407 as a thermosensitive polymer with the ability to undergo a sol-to-gel transition at nasal temperature.

A number of measurements will be carried out to investigate whether the characteristics of the formula are in accordance with the standard requirements for intranasal preparations such as particle size, polydispersity index, zeta potential, rheological study, gelling time, mucoadhesive strength, in vitro permeation study, drug release study, histopathological study and physical stability.

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