Proceedings

CESPT

13th Central European Symposium on Pharmaceutical Technology 2021

Contemporary pharmaceutical technology - addressing challenges of innovative and generic medicinal products

16th-18th September 2021, Gdansk, Poland

www.cespt2021.org
Dear Colleagues, Dear Friends,

On behalf of the Organizing Committee and representing Pharmaceutical Faculty of the Medical University in Gdansk, I am pleased to welcome the participants of the 13th Central European Symposium on Pharmaceutical Technology. After 26 years since the CESPT meetings had started the Symposium is organized in a new, hybrid form. This partly on-line event was not actually our choice was dictated by the conditions of a global pandemic situation. The Covid pandemic did not allow us to meet last year to keep the tradition of the 2-years gap between the meetings. However, we are happy that in September 2021 we are able to invite more than one-third of the participants to attend the Symposium in person, gathering in a traditional way in a main lecture hall of our University. Hopefully this hybrid CESPT is a symbol of recovering from the hard time of pandemic.

I believe that CESPT for years has been one of the Europe’s finest pharmaceutical events. Working on the program of the 13th CESPT we have followed the intention of the previous editions - to give a platform for pharmaceutical sciences in Central European region to bring together colleagues working in the field of pharmaceutical technology both in industry and academia. The conference provides the possibility for the participants to present their results, discuss new developments and the future directions of the pharmaceutical technology, manufacturing and related analysis.

The focus of the meeting is on the topics which are already altering the face of pharmaceutical science and industry: formulation concepts and delivery strategies for improving patients’ compliance, continuous and additive manufacturing, stability and bioavailability of biopharmaceuticals and biorelevant dissolution testing. The challenges generated by these concepts and new achievements in pharmaceutical technology are addressed by the eminent researchers who are attending the symposium.

I am pleased that we have over 130 participants registered. The program contains 12 plenary and keynote lectures and 9 short communications. Not everyone could come to Gdansk due to some health risk that still exists, thus 10 speakers will present the pre-recorded lectures. In the continuous poster session 75 posters will be available for on line presentation and discussion, while 9 posters will be also presented as short videos.

Looking forward to having a fruitful conference we also would like you to enjoy our beautiful city Gdansk. We all do hope that the next CESPT will be organized in a safe Europe, fully in traditional way, with no obligation to include so much on-line activities.

Prof. Małgorzata Sznitowska
President of the Symposium

Head of the Department of Pharmaceutical Technology
Medical University of Gdansk
President of the Symposium: Małgorzata Szmitowska
Co-Presidents of the Symposium: Rok Dreu
Secretary of the Symposium: Bartosz Maciejewski

Honorary Patrons
Marcin Gruchała, Rector of the Medical University of Gdansk
Bożena Karolewicz, President of the Polish Pharmaceutical Society

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István Antal, Hungary | Ildikó Csóka, Hungary | Beatrice Perissutti, Italy
Katerina Goračinova, Macedonia | Maja Simonoska Crcarevska, Macedonia
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Milica Molitorisová, Slovakia | Marija Bogataj, Slovenia | Stane Srčič, Slovenia
Albin Kristl, Slovenia | Mirjana Gašperlin, Slovenia | Jelena Parojčić, Serbia
Svetlana Ibrić, Serbia

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| 15.00 – 15.30 | **Douwe D. Breimer**  
*Leiden Academic Centre for Drug Research, Leiden University, Netherlands:*  
“The future of combination drug therapy: systems pharmacology and the challenges for drug delivery” |
| 15.30 – 17.45 | **Plenary session I:**  
**Chair:** prof. Malgorzata Sznitowska  
*Dept. of Pharmaceutical Technology, Faculty of Pharmacy, Medical University of Gdansk*  
**Formulation concepts and delivery strategies for improving patient’s compliance** |
| 15.30 – 16.15 | **Catherine Tuleu**  
*Department of Pharmaceutics, UCL School of Pharmacy, London, UK:*  
“Kids compliance and beyond = a matter of taste?” |
| 16.15 – 16.45 | Coffee Break                                    |
| 16.45 – 17.15 | **Maria Vertzoni**  
*Department of Pharmacy, National and Kapodistrian University of Athens, Greece:*  
“Regional differences along the gastrointestinal tract and the impact on oral drug absorption” |
| 17.15 – 17.45 | **Sebastian Polak**  
*Faculty of Pharmacy, Jagiellonian University Medical College, Kraków, Poland:*  
*Simcyp Division, Certara UK Limited, Sheffield, UK:*  
“Physiologically based pharmacokinetic modelling to guide drug delivery in special populations” |
Marta Kozakiewicz¹, Anna Junak¹, Adrianna Złocińska², Bożena Karolewicz¹, Karol Nartowski¹.
¹Department of Drug Forms Technology, Faculty of Pharmacy, Wrocław Medical University, Poland, ²Laboratory of Elemental Analysis and Structural Research, Wrocław Medical University, Poland:
“Personalized medicine and application of 3D printing FDM technology in pharmacy”

Alice Biasin¹, Lauretta Maggi², Beatrice Perissutti¹, Dritan Hasa¹, Iztok Grabnar³, Roberto Verardo⁴, Dario Voinovich¹.
¹Department of Chemical and Pharmaceutical Sciences, University of Trieste, Italy, ²Department of Drug Sciences, University of Pavia, Italy, ³Faculty of Pharmacy, University of Ljubljana, Slovenia, ⁴Alphagenics Biotech S.r.l., BIC, Trieste, Italy:
“Lipophilic ginger extract in controlled-release tablets: pharmacokinetics and immunomodulatory effects”

18.15 Welcome reception (AGN building lobby, Medical University of Gdansk)

Friday (17.09.2021)

8.30 – 9.45 Plenary session II: Continuous and additive manufacturing of drug delivery systems
Chair: prof. Andreas Zimmer
University of Graz, Austria

8.30 – 9.15 Johannes Khinast
Graz University of Technology, Institute of Process and Particle Engineering; Research Center Pharmaceutical Engineering GmbH, Graz, Austria:
“High speed technology for the manufacturing of next generation drugs”

9.15 – 9.45 Julian Quodbach
Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University Düsseldorf, Germany:
“Additive manufacturing in pharmaceutics – a new jack of all trades?”

9.45 – 10.15 Coffee Break

10.15 – 11.45 CEEPUS SESSION
Chair: prof. Stane Srčič
University of Ljubljana, Slovenia
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<td>Jelena Parojčič</td>
<td>Department of Pharmaceutical Technology and Cosmetology, University of Belgrade - Faculty of Pharmacy, Serbia; Coordinator of CEEPUS Network CEKA PharmTech: Introduction</td>
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<td>Krisztián Pamlényi¹, Katalin Kristó¹, Dániel Nemes², Ildikó Bácskay², Géza Regdon Jr.¹</td>
<td>“Investigation of stability and permeability of buccal films based on sodium alginate”</td>
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<td>Ivana Ruseska, Katja A. Fresacher, Fabio S. Falsone, Andreas Zimmer</td>
<td>“Tracing the cellular uptake of proticles as delivery systems for miRNA”</td>
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<td>“SMEDDS high-shear wet granulation based on mesoporous carriers for improved carvedilol solubility”</td>
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<td>Luca Éva Uhljar¹, Norbert Radacsi², Rita Ambrus¹</td>
<td><strong>OPTIMIZATION OF ELECTROSPUN NANOFIBER PRODUCTION USING CIPROFLOXACIN AS A MODEL DRUG</strong></td>
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<td>Zsófia Németh¹, Reza Semnani Jazani¹, Dorina Gabriella Dobó¹, Ildikó Csóka¹</td>
<td><strong>FACTORIAL DESIGN-BASED LIPOSOME OPTIMISATION APPLYING VESICLE-MODIFYING MEMBRANE ADDITIVES</strong></td>
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4. Ivana Vasiljević¹, Erna Turković¹, Ilija German Ilić², Andreas Zimmer³, Jelena Parojčić¹, Ivana Aleksić¹

¹Department of Pharmaceutical Technology and Cosmetology, University of Belgrade-Faculty of Pharmacy, Serbia, ²Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ljubljana, Slovenia, ³Institute of Pharmaceutical Sciences, University of Graz, Austria: APPLICABILITY OF SOFTWARE ASSISTED POROSITY EVALUATION IN LIQUISOLID PELLETS CHARACTERIZATION

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| 12.15 – 14.00| Plenary session III: From compendial to biorelevant dissolution testing  
Chair: prof. Géza Regdon Jr.  
Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged, Hungary |
| 12.15 – 13.00| Grzegorz Garbacz  
Physiolution Polska, Wrocław, Poland:  
“Stress after ingest - bio-predictive simulation of the human gastro-intestinal tract” |
| 13.00 – 13.30| Marija Bogataj  
Faculty of Pharmacy, University of Ljubljana, Slovenia:  
“Biopredictive dissolution testing of multiparticulate delivery systems” |
| 13.30 – 14.00| Cornelia Keck  
Department of Pharmaceutics and Biopharmaceutics, Philippus-Universität Marburg, Germany:  
“Dermal drug delivery - novel insides and new perspectives” |
| 14.00 – 15.00| Lunch Break       |
| 15.00 – 16.00| Oral Presentations  
Chair: prof. Beatrice Perissutti  
Dept. Of Chemical And Pharmaceutical Sciences, University of Trieste, Italy |
15.00 – 15.15

Ilenia D’Abbrunzo, Guglielmo Zingone, Beatrice Perissutti, Dario Voinovich, Dritan Hasa
Department of Chemical and Pharmaceutical Sciences, University of Trieste, Italy:
“Role of chirality on the formation of multicomponent crystalline solids containing vinpocetine”

15.15 – 15.30

Barbara Mikolaszek, Damian Roslonowski, Bartosz Maciejewski, Joanna Dlabiszewska, Małgorzata Sznitowska
Department of Pharmaceutical Technology, Medical University of Gdańsk, Poland:
“The effect of a liquid phase on the diffusivity of polyacrylic adhesive transdermal patches”

15.30 – 16.00

Stefan Hellbardt
AptarPharma, Radolfzell, Germany:
“Airless dispensing – safe and convenient drug delivery for semi-solids”

17.30 – 18.30

Guided Sightseeing in Gdańsk
Tour starts at the Mercure Gdańsk Old Town Hotel
Jana Heweliusza 22, Gdańsk

20.00

CONFERENCE DINNER
Filharmonia Restaurant
Ołowianka 1, Gdańsk

Saturday (18.09.2021)

8.30 – 10.30

Plenary session IV:
Approaches to stability and bioavailability of biopharmaceuticals
Chair: prof. Rok Dreu
Faculty of Pharmacy, University of Ljubljana, Slovenia

8.30 – 9.15

Pegi Ahlin Grabnar, Maja Bjelošević
Faculty of Pharmacy, Department of Pharmaceutical Technology, University of Ljubljana, Slovenia:
“Excipients in biopharmaceuticals from perspective of formulation stability and freeze drying process efficiency”
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<td>9.15 – 9.45</td>
<td><strong>Andreas Zimmer</strong>&lt;br&gt;Department of Pharmaceutical Technology and Biopharmacy, University of Graz, Austria:&lt;br&gt;“New mRNA vaccines - is the formulation a miracle?”</td>
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<td>9.45 – 10.15</td>
<td><strong>George Shlieout</strong>&lt;br&gt;1 Pozlab, Złotniki, Poland; 2 Applied Manufacturing Science, Złotniki, Poland:&lt;br&gt;“Challenges and new concepts in formulation of solid dosage forms for biopharmaceutical products”</td>
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<td>11.00 – 11.45</td>
<td><strong>Oral Presentations</strong>&lt;br&gt;Chair: prof. Malgorzata Sznitowska&lt;br&gt;Dept. of Pharmaceutical Technology, Faculty of Pharmacy, Medical University of Gdansk</td>
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<td>11.00 – 11.15</td>
<td><strong>Pavlína Komínová</strong>, Petra Havelková, Petr Zámostný&lt;br&gt;Department of Organic Technology, University of Chemistry and Technology Prague, Czech Republic:&lt;br&gt;“Effect of polydimethylsiloxane additive on process of filling corn starch fillers into hard gelatin capsules”</td>
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<td>11.15 – 11.30</td>
<td><strong>VIDEO POSTERS</strong>&lt;br&gt;1. <strong>Adam Paclawski</strong>, Natalia Czub, Aleksander Mendyk, Renata Jachowicz&lt;br&gt;Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University Medical College, Kraków, Poland:&lt;br&gt;Data-Driven Modeling of Dissolution Process of Poorly Soluble Drugs from Powder Systems&lt;br&gt;2. <strong>Ewelina Łyszczarz</strong>, Aleksandra Pochroń, Renata Jachowicz&lt;br&gt;Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Jagiellonian University Medical College, Cracow, Poland:&lt;br&gt;Optimization of Electrospun Orodispersible Films with Aripiprazole</td>
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3. Jolanta Pyteraf, Witold Jamróz, Mateusz Kurek, Bogna Stachnik, Marian Paluch and Renata Jachowicz
1Department of Pharmaceutical Technology and Biopharmaceutics, Jagiellonian University Medical College, Poland, 2Silesian Center for Education and Interdisciplinary Research, University of Silesia, Poland:
EVALUATION OF FACTORS AFFECTING THE KEToprofen RELEASE FROM 3DP TABLETS

4. Eliza Wolska, Martyna Szymańska, Małgorzata Sznitowska
1Department of Pharmaceutical Technology, Medical University of Gdańsk, Poland,
2Student Chapter of International Society for Pharmaceutical Engineering (ISPE), Poland:
INFLUENCE OF CHOICE OF METHOD AND TEST CONDITION ON THE RESULTS OF DRUG RELEASE STUDY FROM LIPID MICROSPHERES

5. Katarzyna Centkowska, Marta Basztura, Małgorzata Sznitowska
Department of Pharmaceutical Technology, Medical University of Gdańsk, Poland:
TECHNOLOGY OF ORODISPERSIBLE POLYMER FILMS AS MULTIPARTICULATE DRUG DELIVERY SYSTEMS WITH PELLETS – INFLUENCE OF DIFFERENT GRANULES LOADING ON FILM PROPERTIES

11.15 – 11.30
VIDEO POSTERS

11.30 – 11.45
Q&A Session

11.45 – 12.30
Closing Ceremony

Aleš Mrhar
Faculty of Pharmacy, University of Ljubljana, Slovenia:
“CESPT – Past and future”

Małgorzata Sznitowska, Rok Dreu
1Department of Pharmaceutical Technology, Medical University of Gdańsk, Poland,
2Chair of Pharmaceutical Technology, University of Ljubljana, Slovenia:
Closing remarks

12.30 – 13.00
Farewell reception
(AGN building lobby, Medical University of Gdańsk)
Abstracts of Oral Presentations

THE FUTURE OF COMBINATION DRUG THERAPY: SYSTEMS PHARMACOLOGY AND
THE CHALLENGES FOR DRUG DELIVERY

Douwe D. Breimer

Leiden Academic Centre for Drug Research, Leiden University, Netherlands

The prescription of combinations of drugs has always been part of therapeutic practice. However, they were often not based on science based evidence and have lead to undesirable polypharmacy. Recent developments in systems pharmacology indicate a more rational approach to drug combinations. Systems pharmacology deals with the study of drug effects caused by dynamic interactions between several components (targets) of a biological system. It explains why certain complex pathophysiological conditions require multitarget interventions in order to achieve an optimal therapeutic effect. Important examples are combinations of two or more drugs aiming at different targets simultaneously and synergetically (hypertension, HIV, cancer etc). Systems pharmacological principles establish the rational basis for such drug combinations, this in contrast to several combinations that have no more than an empirical background. PK/PD modelling approaches represent the experimental tools to identify the resilience of a biological system as well as its sensitivity to synergetic pharmacological interventions of different compounds administered simultaneously. This synergism is usually obtained if a certain concentration ratio of drugs is maintained in plasma. This in itself represents a challenge for drug delivery, because the requirements for the rate of drug release from the same dosage form may be quite different for the different active ingredients. This may for example be achieved through multilayered matrix technologies or 3D-printing of dosage forms.
Children and young people are not “little adults” but a distinct and heterogeneous patient group whose bodies respond to medications differently from those of adults. Their specific needs and those of their carers, in the context of medicines administration has to be central to the development of the right dosage form that ultimately the sick child will take.

Amongst the multiple barriers to medication compliance in children, this presentation will focus, mainly on understanding desirable attributes for age and ability-appropriate paediatric formulations to support intended treatment outcomes. Palatability being a key characteristic for acceptability, its assessment in vitro and in vivo will be discussed. This will be put in the context of regulatory requirements and industry advances such as solid oral dosage forms for children, within the past 2 decades.
IMPACT OF REGIONAL DIFFERENCES ALONG THE GASTROINTESTINAL TRACT OF HEALTHY ADULTS ON ORAL DRUG ABSORPTION

Maria Vertzoni

Department of Pharmacy, National and Kapodistrian University of Athens, Greece

INTRODUCTION

Oral administration is the most common route of drug delivery. The absorption of a drug from the gut into the bloodstream involves disintegration of the solid dosage form, dissolution of the active pharmaceutical ingredient and its transport across the gut wall. The efficiency of these processes is determined by highly complex and dynamic interplay between the gastrointestinal tract, the dosage form and the active pharmaceutical ingredient. Although the influence of GI physiology on intestinal drug disposition is extensive, the underlying mechanisms often remain difficult to identify. Indirect methods, including deconvolution and PBPK modelling, do not always capture the level of complexity involving a physicochemical event interacting in a variable physiological environment. To assist in understanding drug and drug product behaviour, physicochemical characterization of intraluminal contents collected through local sampling and direct measurement of intraluminal drug concentrations allow integration of all the cogent data [1,2]. This presentation aims to summarize the current knowledge on physiology of the human gastrointestinal tract with emphasis on human studies for the evaluation of the regional drug absorption and the prediction of oral dosage form performance. In vitro and in silico methods to evaluate regional drug absorption will be discussed [3].

REFERENCES

INTRODUCTION

Physiologically based pharmacokinetic (PBPK) modelling and simulation of drug disposition has become an indispensable component of drug development process [1]. By separating information to three independent, yet connected with mathematical model, groups namely drug/formulation, system, and trial design specific respectively one can use already developed and verified model to test various what-if situations. One of the possible options is to utilize such models to assess drug absorption and thus disposition with the focus put on delivery to the biophase in so called special populations. This is of particular interest as running clinical trials in the disease (i.e., liver and kidney insufficiency, psoriasis), genetic (i.e., various CYPs encoding genes variant carriers), pediatric, elderly, or pregnant women populations, to name just a few of them, is difficult if at all possible. By including formulation characteristic, it is also possible to assess to what degree different bioavailability of the API in those populations can be modulated by technological aspects.

MATERIALS AND METHODS

Mechanistic mathematical model of the dermal drug absorption combined with full body PBPK model will be used to exemplify the idea of exploring the influence of physiological and formulation specific parameters on topically applied drug absorption [2]. The MPML MechDermA model combines an extensive database of physiological data with physicochemical and formulation specific parameters thus allowing to simulate drug permeation through the skin and assessing its bioavailability in various populations for different types of dermal formulations [3].

RESULTS AND CONCLUSION

Local skin and plasma drug concentrations were used as the endpoints of interest. The model was able to capture the disposition differences in silico using virtual populations for multiple types of dermally applied formulations (solutions, semi-solids, patches).

REFERENCES

PERSONALIZED MEDICINE AND APPLICATION OF 3D PRINTING FDM TECHNOLOGY IN PHARMACY

Marta Kozakiewicz¹, Anna Junak¹, Adrianna Złocińska², Bożena Karolewicz¹, Karol Nartowski¹

1. Department of Drug Forms Technology, Faculty of Pharmacy, Wrocław Medical University, Borowska 211, Wrocław, Poland
2. Laboratory of Elemental Analysis and Structural Research, Wrocław Medical University, Borowska 211, Wrocław, Poland

INTRODUCTION

Personalized therapies tailored to the patient physiological and pathophysiological conditions, could effectively improve quality of life and reduce the risk of side effects [1]. The paradigm of personalized medicine may become available via application of 3D printing technologies. Currently, one of the biggest challenges of pharmaceutical 3D printing is the lack of commercially available materials. Non-commercial filaments with incorporated APIs (Active Pharmaceutical Ingredients) suitable for FDM (Fused Deposition Modeling) technology can be obtained via hot melt extrusion process (HME), enabling to print variety of complex drug forms in a personalized way. [2]

MATERIALS AND METHODS

Hydrochlorothiazide (HTZ), nicotinamide (NIC), PVA Parteck® MXP, sorbitol Parteck® SI 150 were used. The filaments were prepared using twin screw hot melt extrusion, and a series of placebo tablets and tablets with HTZ:NIC cocrystal were printed using the FDM 3D printer. The obtained filaments and tablets were subjected to thermal stability studies after HME and 3D printing process using TGA and DSC. The structural changes of APIs that may occur during the fabrication process were studied with PXRD and ATR-FTIR.

RESULTS

Drug/polymer/plasticizer blends were designed and processed with HME enabling to form “ready-to-use” filaments for FDM 3DP methods. As a result of co-crystallization, the combination of a high-temperature drug with a lower-temperature co-former allowed us to produce a compound with a melting point corresponding to design processing window and maintaining the pharmacological properties of the drug.

CONCLUSION

Modification of the physicochemical properties of the API by producing a cocrystal enables successful processing of high melting point APIs in HME and 3DP.

REFERENCES


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LIPOPHILIC GINGER EXTRACT IN CONTROLLED-RELEASE TABLETS: PHARMACOKINETICS AND IMMUNOMODULATORY EFFECTS

Alice Biasin¹, Lauretta Maggi², Beatrice Perissutti¹, Dritan Hasa¹, Iztok Grabnar³, Roberto Verardo⁴, Dario Voinovich¹

1. Department of Chemical and Pharmaceutical Sciences, University of Trieste, Italy
2. Department of Drug Sciences, University of Pavia, Italy
3. Faculty of Pharmacy, University of Ljubljana, Slovenia
4. Alphagenics Biotech S.r.l., BIC, Trieste, Italy

INTRODUCTION
The main pharmacological properties of the bioactive constituents of ginger include anti-inflammatory and immuno-modulatory actions. [1-2] This study aims to assess such properties through gene expression profiling and pharmacokinetics after oral administration of controlled-release tablets containing lipophilic ginger extract.

MATERIALS AND METHODS
100 mg of a lipophilic extract of Zingiber officinale (titrated at 17% in 6-gingerol and 5% in 6-shogaol), formulated as a HPMC-based erodible matrix, was given orally to eight healthy volunteers. Besides the pharmacokinetic analysis, total RNA was extracted from the peripheral blood mononuclear cells (PBMCs) and the isolated monocyte, in order to conduct a NGS sequencing (RNA-seq) and a subsequent Gene Set Enrichment Analysis (GSEA) on the generated data, to examine the transcriptional remodelling induced by the extract.

RESULTS
The pharmacokinetic gave the following parameters: Cmax 13.03 ng/ml, Tmax 6.5 h and AUC0-t 154.64 ng/ml*h for 6-shogaol; Cmax 17.97 ng/ml, Tmax 8 h and AUC0-t 130.53 ng/ml*h for 6-shogaol glucuronide. Interestingly, 6-shogaol presented at first an enterohepatic metabolism and then a plateau in the concentration from 4 to 12 h after the administration, possibly due to the controlled-release matrix system. 6-gingerol and 6-gingerol glucuronide were not detected in any plasma samples, probably because of the first-pass effect. Integrated functional analysis performed on the generated gene expression data highlighted a transcriptional remodelling regarding immunomodulatory and inflammatory pathways, such as TNF-α and NF-kB signalling and the pathway for the response to glucocorticoids.

CONCLUSION
This study defined for the first time the pharmacokinetic of the bioactive compounds of ginger contained formulated as controlled-release tablet and provided evidence to support their immunomodulatory and anti-inflammatory properties.

REFERENCES
The current Corona crisis has drastically shown us to what great extent Europe depends on countries, such as China and India, in terms of production of APIs, drugs and medical devices. In a globalized world complete self-sufficiency is – of course – neither possible, nor desirable. However, the current situation shows the need for Europe to become as independent as possible and to bring API production back to Europe – not only to master the current crisis, but also to be able to react in a fast, efficient and autonomous manner to a new health crisis in the future, saving human lives. We thus are planning a new production facility for oral dosage forms (tablets and capsules), which will allow to manufacture high-quality emergency-drugs (e.g. against COVID 19) within a few weeks as soon as a potent API has been identified. The major advantage of RCPE’s High-Speed Technology compared to the traditional approach is the fact that the material flows through the system similar to an assembly line, while the quality of the product is checked in real-time by online sensors and not via lengthy quality lab assessment (Continuous Manufacturing). Production costs can be kept low, as variations in quality are avoided, production plants can be kept small and storage costs are low. This will enable Europe to compete with lower-wage countries like China and India while making the drugs affordable for every patient. Moreover, such facilities are “greener” and thus support another goal of the European Union, i.e., the sustainable development of its economy.
Pharmaceutical additive manufacturing, or 3D printing, is a novel set of technologies for the preparation of dosage forms. Many hopes and promises are connected to the application of this set of techniques. These hopes and promises are directly related to the layer-by-layer manufacturing principle according to easily modifiable computer files. It is frequently mentioned that this would allow an uncomplicated individualisation of dose and dissolution properties by modification of the size and shape of medicines or the combination of multiple APIs in a single dosage form (“flex-dose-combinations”). The comparably low manufacturing speed appears to be ideal for the manufacturing of clinical trial samples. A small footprint would enable various decentralised manufacturing strategies.

Yet how realistic are these scenarios? This presentation will highlight the enabling aspects of additive manufacturing in pharmaceutics but also discuss the open questions that need to be answered before the widespread application of 3D printing may become a reality.
INTRODUCTION

Oral mucoadhesive systems, such as polymer films, are among innovative pharmaceutical products. Buccal polymer films possess many advantages. These systems can be applied in swallowing problems and can also be used in geriatrics and pediatrics [1]. In our earlier work we successfully formulated buccal mucoadhesive polymer films, which contained cetirizine-hydrochloride (CTZ) as API [2]. The present study focused on investigating the stability and permeability of the prepared films.

MATERIALS AND METHODS

Sodium alginate (SA), HPMC polymer films were prepared containing CTZ. The stability of films was studied with accelerated stability test (40 °C ± 2 °C, 75% RH ± 5% RH). Different methods were performed to get information about the changes of the properties of films. During the stability test, thickness, tensile strength (hardness), in vitro mucoadhesivity and permeability were analyzed. Furthermore, the interactions were studied with FT-IR spectroscopy and the changes in the amount of API were also monitored by dissolution study. Cell line permeability study was carried out on TR 146 buccal cells, which were grown on cell culture inserts. Samples of the films were loaded into the upper phase of the inserts and the cetirizine concentration of the lower phase was measured with a spectrophotometer after 1, 2 and 3 h.

RESULTS

It can be seen that citric acid decreased the stability and reduced every physical parameter of the films, but it did not influence the dissolution of API. However, 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 from 4.5% to 5.6% for formulations prepared 1:1 SA:HPMC ratio and from 1.7% to 3.6% in case of SA films without HPMC.

CONCLUSION

In our work, we have successfully formulated CTZ-containing buccal films with adequate stability and appropriate absorption based on cell line permeability studies.

REFERENCES

TRACING THE CELLULAR UPTAKE OF PROTICLES AS DELIVERY SYSTEMS FOR miRNA

Ivana Ruseska, Katja A. Fresacher, Fabio S. Falsone, Andreas Zimmer

1. Department of Pharmaceutical Technology & Biopharmacy, Institute of Pharmaceutical Sciences, University of Graz, Austria

INTRODUCTION

Proticles (protamine nanoparticles) are an up-and-coming strategy for delivery of nucleic acids, such as miRNAs [1]. Despite the many studies on their efficacy as a transfection system, there is a lack of information regarding the intracellular fate of proticles. In order to demystify this black-box, the goal of our study was to investigate the initial steps in the uptake of three types of proticles: albumin- and SERF-decorated, as well as ligand-free proticles in living 3T3-L1 cells.

MATERIALS AND METHODS

The preparation of proticles was described elsewhere [1]. For the preparation of albumin- and SERF-decorated proticles, defined amounts of both proteins were mixed with protamine prior to the miRNA addition. The uptake of proticles was traced in living 3T3-L1 cells, using a combination of DIC and fluorescence microscopy. The quantification of the uptake was done by measuring the fluorescence intensity using a microplate reader. The uptake was tested at different temperatures, as well as in the presence of ATP-depleting agents.

RESULTS

The obtained microscopic images show that uptake of the three types of proticles occurs within the first 15 min of incubation with the cells. Ligand-free proticles tend to localize mostly in and around the nucleus. Albumin- and SERF-decorated proticles show a more even distribution between the nucleus and cytoplasm, which is a desirable outcome for miRNA delivery. The quantitative uptake studies show that SERF-proticles have the highest uptake in 3T3-L1 cells, followed by ligand-free proticles. The results also demonstrate a negligible difference between the uptake at 4°C and 37°C, as well as in the presence of ATP-depleting agents, which might suggest an energy-independent mechanism of uptake.

CONCLUSION

The uptake of proticles in cells is a rapid process and part of it might be due to direct translocation through the cell membrane. The attachment of albumin and SERF to the proticles shifts their intracellular behaviour in a way that might be favourable for miRNA delivery in the cell cytoplasm. Future studies will focus on better defining the uptake process and cellular localization of proticles.

REFERENCES

SMEDDS HIGH-SHEAR WET GRANULATION BASED ON MESOPOROUS CARRIERS FOR IMPROVED CARVEDILOL SOLUBILITY

Mila Kovačević, Katarina Bolko Seljak, Alenka Zvonar Pobirk, Ilija German Ilić

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

INTRODUCTION

Self-microemulsifying drug delivery systems (SMEDDS) are one of most promising formulation strategies developed to improve solubility of poorly water soluble drugs, such as carvedilol, among others [1]. SMEDDS are originally in liquid state, so it would be beneficial if they could be transformed into solid form [2]. To achieve that, mesoporous carriers are most convenient due to high liquid load capacity, while maintaining characteristics of dry, free flowing powders [3].

MATERIALS AND METHODS

SMEDDS granules were prepared manually, by wet granulation method. Granulation dispersion containing microemulsion with SMEDDS/water ratio of 70/30 and PVP K25 used as binder, was added to six different mesoporous carriers. With regard to amount of SMEDDS incorporated in granules, their flow properties and in vitro carvedilol release, Neusilin® US2 and Syloid® 244FP were chosen as the most suitable carriers for wet granulation using high-shear granulator. These granules were further used for production of orodispersible tablets (ODTs), with carvedilol content of 12.5 mg.

RESULTS

All of produced granules had high SMEDDS content which represented 37-66% m/m of granule weight. All granules showed excellent flow properties (according to angle of repose criteria in Ph. Eur. 10th Ed.), preserved self-microemulsifying properties upon dispersion and therefore improved carvedilol in vitro release. Ultimately, a self-microemulsifying ODTs weighing 845 mg, met the pharmacopoeial criteria for disintegration (<51 s) and friability (<0.22 %), simultaneously showing slightly slower carvedilol in vitro release than the granules.

CONCLUSION

Granules with Neusilin® US2 and Syloid® 244FP showed the best flow properties and high SMEDDS loading of ≈60% m/m of SMEDDS incorporated in granules produced by high-shear granulator. Excellent flow properties enabled compaction and preparation of ODTs with adequate mechanical characteristics which preserved self-microemulsifying properties, responsible for improved in vitro carvedilol release.

REFERENCES

STRESS AFTER INGEST – BIO-PREDICTIVE SIMULATION OF THE HUMAN GASTRO-INTESTINAL TRACT

Grzegorz Garbacz
Physiolution, Polska

INTRODUCTION
The presentation will focus pragmatic question is what are the truly “bio-predictive” conditions of the human gastro intestinal tract and how can we simulate them? Key issues of the realistic simulation of the GI transit will be introduced.

MATERIALS AND METHODS
The development of bio predictive dissolution tests aims at realistic simulation of mechanical and chemical conditions of the GIT. It can be successfully performed using simple, abstract dissolution models such as the bio-relevant dissolution stress tester, or its later modifications such as Dynamic Open Flow-Through Apparatus, and recently developed Universal Modular Platform. Although, the models do not reflect the anatomy of the GI tract, they can successfully simulate individual physiological factors via working principles and parametrization [1].

RESULTS
The variability of the physiological factors relevant for the dissolution performance of oral medicines such as pH pressure and temperature will be discussed in the context of literature and experimental data. Clinically relevant examples of bio-predictive dissolution tests generated using abstract models will be presented and discussed.

CONCLUSION
The use of the bio-predictive methods supports of the rational, physiology driven development of oral medicines and enables identification of their undesired drug delivery performance in the preclinical stage. Consequently it increases the reliability and biopharmaceutical quality of oral drugs, effectiveness of the pharmacotherapy and significantly reduces the dosage forms related side effects and therapy failures.

REFERENCES
After oral administration of multiparticulate dosage form pellets / small particles leave the stomach in a wide time interval and thus all pellets are not exposed to gastric medium for the equal times. In cases when drug release differs in the media of stomach and small intestine, gastric residence time is extremely important for drug release and consequently also its absorption. In the scope of the present work literature data on pellets gastric emptying were analysed and an approach how to implement them in dissolution testing suggested. The aim of this work was to simulate the pellets gastric emptying and its influence on drug dissolution in *in vitro* dissolution experiments by the aid of mathematical/statistical approach, and thus reliably predict the drug and the multiparticulate dosage form performance after administration.

Literature search showed that variability of individual gastric emptying profiles of pellets is huge, from very fast one bolus profiles up to lag-time followed by the slow emptying where the whole process is completed in two or three hours [1]. In some individual profiles emptying in two consecutive boluses can be seen with the time interval between boluses of approx. 2 hours which corresponds to the length of one MMC cycle. Pellets gastric emptying profiles were described using different mathematical models; double Weibull model described individual profiles best. Gastric emptying interval of each profile was then divided in shorter intervals and fractions of pellets emptied in each shorter interval calculated by the aid of developed models. For each shorter interval, dissolution test was performed keeping the pellets in gastric medium for the mean time of interval. Each obtained dissolution profile was multiplied by the corresponding fraction of pellets and predicted *in vivo* dissolution profile calculated as a sum of all thus weighed profiles. In further work predicted *in vivo* dissolution profiles were compared with absorption profiles from human bioavailability studies [2,3]. Enteric coated pellets and pellets containing drug with pH dependent solubility were included in these studies. In most cases the described approach which basis on physiological gastric emptying mechanisms, gave good *in vitro in vivo* correlation which was not possible to be obtained considering only one residence time in gastric medium.

**REFERENCES**

Dermal application of active compounds is routinely exploited in pharma and cosmetics. However, effective penetration is often not achieved and thus the use of innovative vehicles and/or carrier systems is required to yield sufficient results. The prediction of the penetration efficacy from different formulations is often not possible and therefore formulation development today is still a “trial and error” approach. Another hurdle is the lack of fast and easy to perform methods that allow for a reliable discrimination between good and bad penetrating samples in early formulation development.

Recent studies showed that penetration testing on the ex-vivo porcine ear model with subsequent digital image analysis is a powerful tool for the space- and time-resolved determination of the dermal penetration efficacy [1]. In addition, by assessing the stratum corneum thickness – it is also possible to determine not only the penetration efficacy but also the influence of the formulation on the skin hydration [2-4]. This combination enables a holistic interpretation of data and allows for linking formulation properties to skin properties and dermal penetration efficacy at the same time. With this it was found that the proposed mechanisms of dermal penetration (passive diffusion into and through the skin and penetration via the hair follicles) should be re-considered [2-7].

The new understanding of dermal penetration involves solvent drag mechanisms and particle assisted dermal drug delivery via the formation of an aqueous meniscus between particles and skin which promotes a long-lasting, high local concentration gradient. The combination of both effects and the use of mechanical skin treatments to modulate the skin properties opens new perspectives for highly effective and targeted dermal drug delivery.

REFERENCES

3. Pelikh O and Keck CM, Nanomaterials 2020, 10(11), 2323
INTRODUCTION

Chirality plays an essential role in pharmaceutical materials science as it represents a distinctive feature found in many molecules and their relative crystals.[1] Several chiral molecules often show difficulty on forming multicomponent solids. This study explores the propensity to form multicomponent crystalline solids of the chiral drug vinpocetine (a synthetic drug known for its potent neuroprotective effect) in the presence of chiral coformers. Malic acid was chosen due to the low toxicity and because it allowed to investigate the crystallization of vinpocetine in the presence of each enantiomer (D and L-malic acid) and the racemic form.

MATERIALS AND METHODS

Several solution-based and solid state mechanochemical cocrystallization experiments were performed. Mechanochemical liquid-assisted grinding was used for understanding the role of solvent on the crystallization of the multicomponent system.[2] Neat and polymer-assisted grinding [3] were also considered.

RESULTS

During the crystallization studies performed in this study, the multicomponent system showed an enantiospecific behaviour: only the solid consisting of vinpocetine and L-(−)-malic acid crystallized, while the solid containing D-(+)-Malic acid gave an amorphous solid. Both solution-based and mechanochemical crystallization experiments gave similar outcomes. Dissolution tests were also carried out. Different solid forms (either crystalline or amorphous) showed a significant improvement of the dissolving performance when compared to raw vinpocetine. Interestingly, the dissolution profile of the crystalline multicomponent solid was superior compared to the amorphous product, highlighting the importance of the physical status (amorphous or crystalline) during the preformulation studies of innovative dosage forms.

CONCLUSION

Chirality can significantly affect the propensity to form multicomponent solids, including the propensity to form a crystalline or amorphous system. The new solid forms of vinpocetine showed an important improvement of the dissolution rate in comparison to the pure drug.

REFERENCES

THE EFFECT OF A LIQUID PHASE ON THE DIFFUSIVITY OF POLYACRYLIC ADHESIVE TRANSDERMAL PATCHES

Barbara Mikolaszek, Damian Rosłonowski, Bartosz Maciejewski, Joanna Dłabiszewska, Małgorzata Sznitowska

Pharmaceutical Technology Department, Medical University of Gdańsk, Poland

INTRODUCTION

Pressure-sensitive adhesive polymers (PSA) are a basic excipient used for the formulation of transdermal patches. The material’s diffusivity for an active substance plays a crucial role in the patch performance, including drug release and adhesion [1, 2]. To modify release rate of the patch only limited number of excipients can be used, because of excipient-PSA-drug interactions [3]. The aim of this study was to assess the effect of liquid additives on the diffusivity properties of the polyacrylate matrix for a model drug – indomethacin.

MATERIALS AND METHODS

Patches were prepared using the casting technique. In the first step indomethacin (5%) was mixed in a planetary mixer with liquid additive (isopropyl myristate MIP, polyethylene glycol PEG, propylene glycol PG, triacetine TA or triethyl citrate TEC; 10% w/w), followed by PSA polymer addition (Duro-Tak 87-2852, Henkel). Indomethacin release rate from a modified matrices was evaluated with in vitro dissolution test (Ph.Eur. apparatus 5, paddle over disk, 75 rpm at 37°C, medium phosphate buffer 7.4). Scanning electron microscopy, optical microscopy and Raman confocal microscopy imaging experiments were performed to evaluate surface of the patches.

RESULTS

Transparent patches of 150 μm thickness were obtained, consisting of 2 mg/cm² of indomethacin. Among liquid additives, only PEG created net-like structure on the patch surface, which was imaged with SEM. Homogenous distribution of a dissolved drug within the surface was found, but for MIP and PEG the concentration was considerably higher. Only in case of TEC considerable number of indomethacin particles were visible, with a single particles located superficially, as confirmed with SEM and Raman imaging. The most pronounced increase of the release rate of indomethacin after 48h was also noted in the presence of MIP and PEG (0.70 and 0.92 mg/cm², respectively; 0.5 mg/cm² for a pure patch).

CONCLUSION

It has been demonstrated that in case of indomethacin diffusivity of the PSA varied dependably on the liquid phase type. The mechanism of the promotion of a drug release seems guarded by the interaction between the film-forming polymer and the additive.

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REFERENCES

INTRODUCTION

Topical drug delivery for treatment of skin conditions enjoys increased interest due to improved access and tolerability vs. other routes of administration. Airless dispensing technology is on the rise for development projects of topical drugs.

RESULTS

The majority of topical skin medication are medium- to high-viscous in nature. Reliable and convenient dispensing of such semi-solids are a challenge with commonly used packaging, such as tubes or lotion pumps. Airless technology overcomes such challenges by equilibrating the dispensed product with moving elements, rather than incoming air. This is beneficial as air bubbles in viscous products interfere with dose reliability, emptying, and user convenience. Dosed Airless Drug Delivery Systems offer excellent protection and consistent dosing of semi-solid drug products. Patients appreciate the clean and convenient dispensing, support of mobile lifestyle, and the appealing design, modern Airless dispensers come with.

In addition, Airless Drug Delivery Systems support shelf differentiation, sustainability goals, and can help accessing a connected health environment.

Partnering with experienced device manufacturers ensures maximizing the benefit of Airless Drug Delivery Systems avoiding technical challenges. By offering associated services and expertise in managing the changing regulatory requirements, Aptar Pharma is well positioned to help de-risking and accelerating drug development projects up to successful market launch and beyond.

CONCLUSION

Airless technology is increasingly used in the development of semi-solid drug products. The protection of drug product, safe and reliable dosing, and the convenient and clean delivery by Airless Devices is recognized by pharmaceutical manufacturers around the world.

Partnering with experienced providers of Airless Drug Delivery Systems like Aptar Pharma, ensures maximizing the benefit of Airless technology avoiding technical and regulatory challenges.
EXCIPIENTS IN BIOPHARMACEUTICALS FROM PERSPECTIVE OF FORMULATION STABILITY AND FREEZE DRYING PROCESS EFFICIENCY

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INTRODUCTION

Excipients in biopharmaceuticals can contribute significantly to the stability of a biologically active ingredient, and indirectly they can also affect the time needed for lyophilisation. In addition to sucrose and trehalose, novel stabilisers with higher glass transition temperature of maximally freeze-concentrated solution (Tg') and collapse temperature (Tc) have undergone extensive studies with the aim to perform shorter primary drying phase at higher temperature [1]. Crystalline bulking agents in lyophilized biopharmaceutical formulations provides an elegant lyophilized cake structure and allows aggressive primary drying conditions. The aim of the research work was to study the influence of different mannitol to sucrose ratios and monoclonal antibody concentrations on mannitol physical form established during lyophilisation [2]. High mannitol to sucrose ratios are required to ensure bulking agent crystallization during freeze drying process [3]. Therefore several amino acids as potential alternative bulking agents in low amino acid to sucrose ratios were investigated.

MATERIALS AND METHODS

Formulations with different excipients and different mAb concentration were subjected to lyophilisation. Solutions and freeze-dried products were characterised using differential scanning calorimetry (DSC), powder X-ray diffraction (XRPD), micro-flow imaging (MFI), size exclusion chromatography (SEC), cation exchange chromatography and dynamic light scattering (DLS). Reconstitution time of lyophilisates was evaluated.

RESULTS

The limiting factor for the implementation of mannitol as crystalline bulking agent in the lyophilized mAb based formulation is the content of the amorphous stabilizer and its molar ratio to protein. The ratio between phenylalanine/isoleucine and sucrose of 1:4 is high enough to obtain lyophilisates with acceptable appearance and stability. Isoleucine shows a good potential for mannitol replacement in low-concentrated protein formulations.

CONCLUSION

The selection of excipients in freeze-dried products should be critically evaluated in order to achieve acceptable critical quality product attributes and to provide stability of mAbs.

REFERENCES

mRNA vaccines currently were introduced and approved as SARS-CoV-2 vaccines in up to 96 countries worldwide. Pfizer/BioNTech: BNT162b2 (Comirnaty), the Moderna: mRNA-1273 referred to as Spikevax, and the equivalent galenic formulation Takeda: TAK-919 are the first mRNA vaccines on the market. In total 7 vaccines were approved for human use by WHO (Aug. 2021). These include also vaccines based on a non replicating viral vector technology or the more classical approach to use inactivated viral material. In addition to these already established RNA products next generation self-amplifying RNA (saRNA) are in clinical trials. Nevertheless the approved vaccines came to market more or less one year after the spreading of the SARS-CoV-2 virus which was communicated as a great success of research and development which speeded up during the pandemic situation and, therefore, many people, but also the legal authorities were scared about the new RNA technology which was not “long-term” tested as vaccines before and which may have unknown side effects.

The aim of this talk will be to convince the audience that this RNA technology and galenic formulation is not that new as it was communicated to public media and it was also not a revolution in science. Indeed, most of the research which is now commercialized is based on the idea of lipofection which was published by Felgner and Ringold [1] for the first time in 1989. Since the last 30 years this technology was constantly improved and now the so called lipid nanoparticles are nucleic acid (DNA or RNA) complexes with cationically charged lipids. A typical lipid nanoparticle formulation is composed of a pH-responsive lipid bearing tertiary or quaternary amines to form a complex with the polyanionic mRNA. In addition neutral helper lipids such as zwitterionic lipid [i.e. 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) or 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)] and/or a sterol lipid (i.e., cholesterol) are added to stabilize the lipid (bi)layer of the lipid nanoparticle and to enhance mRNA delivery efficiency. To improve the colloidal stability in biological environments a polyethylene glycol (PEG)-lipid which is reducing a specific absorption of plasma proteins and forming a hydration layer at the surface of the nanoparticles is also part of the formulation [2].

In conclusion, mRNA formulations are not a miracle and the presentation will provide an update of the formulation and production technology of these RNA products.

REFERENCES
CHALLENGES AND NEW CONCEPTS IN FORMULATION OF SOLID DOSAGE FORMS FOR BIOPHARMACEUTICAL PRODUCTS

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INTRODUCTION

Biologics and especially purified proteins are formulated in a liquid form since physical and mechanical stresses induced losses of biological activities, reduced content of pure API and led to creation of new impurities (e.g. aggregation). Impurities in general are divided in Process-related impurities and Product-related impurities.

The case studies of 2 different purified proteins which should be administered orally will be discussed. The products were formulated by using different technology platforms and the results are compared to select the process preventing creation of any new impurities.

MATERIALS AND METHODS

Formulating 2 pharmaceutical industrial purified proteins is requested for pre-clinical and phase I clinical study. Titration biological activity methods are used. In addition, RP-HPLC and SEC methods and Sedimentation Velocity Analytical Ultracentrifugation (SV-AUC) are used to determine the content, the impurity and aggregation profiles of the APIs and formulated products.

RESULTS

The results of this research work clearly showed that for protein A classical manufacturing process like extrusion will lead to a significant reduction of the biological activity and create at the same time new impurities. Whereas the appropriate process parameters of the non-parails technology (API layering) led to a comparable biological activity and impurity profile compared to the API used. The stabilization of protein B was not possible even by using the API layering technology without using stabilizers. Stabilizer screening was done by using different excipients and the best option was observed when using non-reducing sugar.

CONCLUSION

Formulating the investigated purified proteins into solids by using classical manufacturing processes led to biological activity losses and to creation of new impurities.

Processes with minimal physical and/or mechanical stresses are not always an option.

The combination of stress-free processes and the proper stabilization strategies is an option for producing formulation without activity losses and without additional impurities (due to aggregation).
INTRODUCTION

Hard gelatin capsules are commonly used dosage forms in pharmaceutical industry. For larger-scale productions, there are several types of automated capsule filling equipment. The two most used types of filling machines operate using dosing disc and dosator concepts. Each type uses a different operating principle and works under different conditions. Therefore, requirements on powder rheological properties can be quite complex and these properties need to be studied and adapted to a specific filling technique for a failsafe operation. The objective of this contribution is to deliver a case study dealing with the investigation and optimization of a real powder mixture for capsule filling.

MATERIALS AND METHODS

The mixture composed of active pharmaceutical ingredient (API, non-disclosed, 5.06 w/w %), corn starch (CS, 94.75 - 94.93 w/w %) and liquid dimethicone (D, 0.01 - 0.19 w/w %) was prepared in several steps including high-shear blending of a premix of D and defined amount of CS, preparing the active mixture (API and CS) and mixing the premix, the active mixture, and the remaining amount of CS together to obtain the final mixture. The rheologic properties were characterized by the powder rheometer FT4. The main focus was on the used type of corn starch (native or partially pregelatinized), the impact of premix composition, and the way of its preparation. Thus, next to the original formulation, several modifications were carried out to affect the premix internal structure that reflected in the rheological properties of the final mixture. However, the final composition was identical for all prepared mixtures.

RESULTS

Results revealed the effect of both applied types of CS and premix modification approach on the mixture rheological properties. Better rheological properties were observed for mixtures containing partially pregelatinized starch. Each type of premix modification affects D - CS interactions differently, resulting in formation of agglomerates having diverse mechanical properties, and thus also diverse rheological properties of the final mixture.

CONCLUSION

These findings indicate the possibilities to adjust rheological properties of powders with dimethicone application. By modifying the formulation and some process parameters, it is possible to tailor the rheological properties and adapt them to a specific filling technology. This can be of great practical importance, as it could allow the smooth-running filling of given mixture using devices with different operating principles.
Abstracts of Poster Presentations

DATA-DRIVEN MODELING OF DISSOLUTION PROCESS OF POORLY SOLUBLE DRUGS FROM POWDER SYSTEMS

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INTRODUCTION

The dissolution process of active pharmaceutical ingredients plays a critical role in terms of therapy effectiveness. Over the last decades an increasing number of poorly water-soluble APIs introduced into therapy or being under development is a great challenge for pharmaceutical technology. Fast and effective development of dosage forms characterized by optimal dissolution process is crucial for new therapies [1]. At the same time rise of advanced computational methods classified as machine learning and artificial intelligence (AI/ML) could be successfully applied to develop predictive models for multidimensional and complex problems within the pharmaceutics field [2].

MATERIALS AND METHODS

The database was created based on in-house data expanded by information harvested from literature. Every record represented full characteristics of formulations, including qualitative and quantitative composition, production, and dissolution process characteristics. A wide range of AI/ML tools like artificial neural networks, Random Forest, fuzzy logic, and genetic programming were applied to develop an optimal model.

RESULTS

For research purposes database composed of 2626 records describing 314 unique powder systems was created. Through extensive feature selection computations, input vector size was reduced from 3153 variables to 30, and over 1 000 000 models were created and tested according to 10-fold cross-validation method. Among them, two-layer artificial neural network showed the best generalization ability resulting in root mean squared error RMSE =17.10 and coefficient of determination $R^2=0.72$.

CONCLUSION

Applied data-driven methodology led to a general predictive model with acceptable performance for the given problem. Moreover, through the modeling procedures, qualitative and quantitative knowledge was discovered in the form of crucial variables sets and their interrelationships.

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REFERENCES

MESOPOROUS SILICA-BASED PELLETS FOR ORAL DELIVERY OF DOXYCYCLINE HYDROCHLORIDE

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INTRODUCTION

The amorphous silica in the form of colloidal silicon dioxide (colloidal silica) is widely used in pharmaceutical technology as a glidant, anticaking agent, emulsion stabilizer, and tablet disintegrant. Another type of amorphous silica, considered as a promising drug delivery system, are mesoporous silica materials (MSMs). Due to the high porosity and ordered pore arrangement, MSMs offer many features such as efficient drug adsorption, better control of drug release profile, and the enhancement of drug bioavailability.

Herein, we investigated the influence of use of mesoporous silica SBA-15 with adsorbed model water-soluble drug (doxycycline hydrochloride, DOX) on the drug release rate from the pellets, compared with microcrystalline cellulose-based DOX pellets (MCC-pellets).

MATERIALS AND METHODS

Mesoporous silica SBA-15 powder was synthesized using the sol-gel method proposed by Zhao et al. [1]. DOX was adsorbed onto the SBA-15 using adsorption from the concentrated drug solution [2]. The pellets were obtained on a laboratory scale in Caleva Multi Lab apparatus using DOX-loaded SBA-15 powder and excipients: microcrystalline cellulose, ethyl cellulose, magnesium stearate, and ethanolic solution of polyvinylpyrrolidone. For comparative purposes, conventional MCC-pellets with DOX were obtained in the same manner. The obtained pellets were examined in terms of physical properties (particle size distribution, hardness, friability, disintegration time, drug content) and dissolution test.

RESULTS

The obtained SBA-15-pellets were characterized by satisfactory physical properties, similar to the MCC-pellets. The prolonged 12 h drug release was observed for SBA-15-pellets which was 2 times longer compared to MCC-pellets. The MCC-pellets were characterized by high burst release due to the rapid dissolution of DOX particles, whereas the observed reduction of initial drug release from SBA-15-pellets was caused by the drug loading into the mesopores of SBA-15.

CONCLUSION

The obtained DOX-loaded mesoporous silica pellets may represent a novel solution in the development of prolonged release formulations for water-soluble drugs. However, further investigations are required to reduce the initial burst release of the drug. The fluidized bed coating and tableting of the pellets will be performed in due course.

REFERENCES

EFFECT OF THE TYPE OF LACTOSE ON AERODYNAMIC PROPERTIES OF INHALATION POWDER CONTAINING ACTIVE SUBSTANCE

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INTRODUCTION

With the increasing knowledge of the physiology of the lungs and respiratory system diseases, drugs delivered directly to the lungs (PDD - Pulmonary Drug Delivery) are becoming an important alternative not only in local but also systemic therapy [1]. Currently, the most common form of inhalation product are inhalation powders administered with the use of the so-called powder inhalers (DPI). Inhalation powders mainly consist of an active substance with appropriate aerodynamic properties (size 1 - 5 μm) and carrier particles - most often lactose (coarse fraction), which improve powder dispersion and flowability. Micronized drug substance (API) particles adhere to the surface of the carrier particles during the mixing operation. The aerodynamic properties of the inhalation powder are characterized, among others, by: APSD - aerodynamic particle size distribution and FPD - fine particle dose, determined by the pharmacopoeial method, using a cascade impactor.

MATERIALS AND METHODS

The formulations were prepared in a high-shear mixer under the set mixing conditions.

Different types of lactose were used, including mixtures of coarse and fine lactose (d50 <10 μm or d50 <5 μm). For prepared formulations FPD and APSD were determined on the Next Generation Impactor (NGI). The amount of active ingredient from individual cups of NGI was determined by HPLC. Particle size and morphology were determined using SEM.

RESULTS

The addition of fine lactose significantly increases the value of the FPD parameter. The highest FPD values are obtained when the addition of micronized lactose (d50 <5 μm) with a particle size distribution similar to the particle size distribution of the API X is used.

CONCLUSION

A significant improvement in the inhalable dose size (FPD) for the inhalation powder containing the active substance X is obtained when micronized inhalation lactose (d50 <5 μm) is used. It was confirmed that the saturation of the active sites of the base lactose by fine lactose significantly improves the aerodynamic properties of the active substance X (FPD and APSD).

REFERENCES

IMPROVING THE OXIDATIVE STABILITY OF OILS THROUGH EMULSION ELECTROHYDRODYNAMIC PROCESSING

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INTRODUCTION

Encapsulation is one of the main strategies for protecting oils against oxidative degradation and incorporating them into food products. [1] Electrohydrodynamic processes (EHDP) – electrospraying and electrospinning – with ambient temperature and possible use of non-toxic solvent present an optimal method for encapsulation of oils (thermolabile and oxygen sensitive substances) from an o/w emulsion. [2] Polymers and solvents used, as well as process parameters, require careful selection in order to obtain repeatable results as they have a direct influence on the morphology of the product. [3] Here, several combinations were tested to create the emulsions – 5/7/10wt% pullulan and 20/25/30wt% dextran 70 with the addition of 1wt% WPC, with the oil load being a constant 2wt%.

MATERIALS AND METHODS

Materials used were linseed oil; polymers: pullulan, dextran 70, WPC (whey protein concentrate) and solvents: water and ethanol. Emulsification was performed at 3000 rpm for 10-minute cycles. The emulsions were evaluated using an optical microscope. The EHDP setup was equipped with an 18 G needle. The obtained product was analysed using TGA/DSC, ATR-FTIR and SEM. Furthermore, acid and peroxide values were measured.

RESULTS

Oil-loaded beads and fibers were generated by electrohydrodynamic processing. Pullulan, dextran 70 and WPC aqueous/ethanol solutions were used to emulsify the susceptible to oxygenation linseed oil. The obtained products showed greater oxidative stability in comparison to non-encapsulated oils. The morphology of the products obtained indicated effective oil encapsulation.

CONCLUSION

Electrohydrodynamic emulsion processing is an applicable technique to produce oil-based capsules and fibers on a micro scale. The capacity of the emulsion to be sprayed or spinned depends on oil load, polymer selection and concentration, as well as the flow rate, the voltage applied and the distance between the needle and the collector.

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INTRODUCTION
Bosentan is a dual endothelin receptor antagonist used for the oral therapy of pulmonary arterial hypertension. Recent clinical studies have pointed out its anti-inflammatory and antiviral effect [1]. Yet, the drug is poorly soluble in water, and therefore; its bioavailability is limited (50 %). The aim of this study was to enhance the solubility of bosentan by vitrification of the crystalline drug in the high energy ball milling process.

MATERIALS AND METHODS
Bosentan monohydrate was kindly donated by Polpharma S.A. (Poland). A planetary ball mill Pulverisette 7, Fritsch (Germany) was used to vitrify the drug. A DSC Q1000 (TA Instruments, France), a PanAnalytical X’Pert PRO MPD diffractometer (Netherlands) and a Nicolet iS5 (USA) ATR-IR spectrometer were used to characterize its solid-state properties. Drug dissolution was studied in fasted conditions using simulated fluids either gastric or small intestinal in a paddle apparatus, Hanson Research Dissolution Station Vision Elite 8 (USA) equipped in a set of small vessels of 150 mL. An HPLC-DAD system Agilent 1260 Infinity (Germany) was used to quantify bosentan dissolved.

RESULTS
Both diffractograms and heat flow curves confirmed the vitrification of bosentan under milling. It was found that the milling time of 2 h was enough to fully vitrify bosentan monohydrate (Tg = 82 °C). There was no recrystallization of the amorphous form while heating up to 190 °C, which indicates high thermal stability. The amorphization kinetics was determined and the experimental data were fitted to the relaxation law ($r^2= 0.956$). Dissolution profiles showed that the amorphous form of the drug dissolved faster than its semi-crystalline or crystalline counterpart. Yet, recrystallization of the drug was observed at low pH. The impact of milling time on the concentration of bosentan dissolved was shown as well. The best properties had bosentan milled for 2 or 4 h. Longer milling time did not result in a further increase in the concentration of bosentan dissolved.

CONCLUSION
High-energy ball milling could be used to vitrify bosentan. The amorphous form gave the opportunity to enhance the dissolution of bosentan.

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SOLID LIPID NANOPARTICLES OR POLYMERIC NANOPARTICLES: HOW TO MENAGE ORAL PERMEATION OF A MOLECULE ACTIVE IN MULTIDRUG-RESISTANT TUBERCULOSIS

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INTRODUCTION
Recently a new compound, SS13, has been synthesized as a potential efflux inhibitor [1]. However, SS13 is insoluble in different simulated gastrointestinal media; thus, its oral permeation is limited. In this work, solid lipid nanoparticles (SLNs) and polymeric nanoparticles (NPs) have been prepared to increase the oral bioavailability of SS13.

MATERIALS AND METHODS
SS13 anti-mycobacterial activity, chemical-physical properties, and pharmacokinetic on Sprague-Dawley rats after an intravenous infusion of 0.6 ml of compound solution were studied. SLNs, consisting of Witepsol E85 and Gelucire 44/14, and NPs composed of poly (lactic-co-glycolic acid) were prepared with a solvent emulsification evaporation method [2]. The chemical-physical characteristics of both nanoparticles were evaluated. SLNs ex vivo permeation, using 12-well cell culture plates suitably modified (project INCREASE SARDINIA 2016-17, protocol number 31351, University of Sassari) on the intestinal mucosa and cytotoxicity were studied. NPs permeation and pharmacokinetic of are ongoing.

RESULTS
SS13 increases the antitubercular activity of several drugs. Pharmacokinetic parameters (concentration at the end of infusion: 30μg/ml; AUC: 1134±65μg-ml-1min; half-life: 28.7±0.9min; clearance 0.71±0.04 ml-min-1-kg-1) indicate a poor aptitude of the compound to migrate to peripheral tissues. About 90% of SS13 was found in the SLNs. They can increase the ex vivo permeation of SS13 through the intestinal mucosa (70%) if compared to pure compound (3%) and affect the Caco-2 viability in a dose-dependent manner. NPs, (particle size 281.2±17.57 nm; PI 0.114±0.043) are stable if stored at 4°C and are able to load SS13. Based on FTIR studies we may suppose the compound entrapment in NPs. Results of nanoparticle permeation and pharmacokinetic will be described.

CONCLUSION
These promising results support the potential application of these nanocarriers for increasing the oral permeation of SS13 in multidrug-resistant tuberculosis management.

REFERENCES
TABLETING PERFORMANCE AND EVALUATION OF THE MECHANICAL ATTRIBUTES OF THE MINITABLETS CONTAINING RIVAROXABAN

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INTRODUCTION

Orodispensible minitablets (ODMTs) are potential novel drug form intended for pediatric or geriatric groups of patients [1]. The aim of this study was to evaluate selected physical attributes of the ODMTs containing 0% (placebo) 5% and 50% w/w of a model drug (rivaroxaban) obtained on a hydraulic-single station and rotary tablet press. The ODMTs critical parameters were determined with compendial methods and with an application of texture analysis. Finally, tabletability, compressibility and compactibility were evaluated and compared for each type of equipment and ODMT formulation.

MATERIALS AND METHODS

ODMTs of 2 mm diameter and weight of 6.0 mg containing micronized (d90 < 20 μm) and coarse grade (d90 < 200μm) rivaroxaban (ZHEJIANG HUAHAI), Granfiller-D215 (DAICEL) and magnesium stearate (FACI), were prepared on rotary press Pressima AX (IMA) and hydraulic-single station press NP-RD10A (NATOLI), equipped with 13-tip punches (NATOLI). Evaluation of physical attributes was conducted with hardness tester TBH225D, disintegration time tester ZT322 (ERWEKA), and texture analyzer Autograph AGS-X (SHIMADZU).

RESULTS

A mass variation (MV) was generally higher in the placebo MT obtained on hydraulic-single station press (RSD=1.91% for PL-Kilian whereas 3.72% for PL-Natoli). An application of coarse grade API (0%, 5% and 50% w/w) did not increase MV (3.72%, 3.57% and 3.24% respectively). The opposite trend was found for the tabletting process on the rotary press (1.91%, 2.31% and 3.24%, respectively). Resistance of crushing of the ODMTs was significantly higher (in the range 174-204%), whereas SD value [%] was significantly lower in the case of the texture analyzer application in comparison to the compendial method.

CONCLUSION

A rotary tablets press provides more reliable and repeatable results in comparison to a single station press. The use of micronized API in the amount of 50% w/w might be problematic due to the poor flowability of the powder blend. It was revealed that the texture analysis is more sensitive to discriminate MT physical attributes like hardness and disintegration time.

REFERENCES

PROTEIN UNFOLDING ON CATION EXCHANGE RESINS DETECTED BY A HIGH THROUGHPUT FLUORESCENCE METHOD

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INTRODUCTION
A fast method for assessment of protein stability adsorbed on ion exchange chromatographic resins has been developed. The method exploits a real time polymerase chain reaction equipment to determine the temperature of protein phase transition, i.e., the so called melting temperature, based on differential scanning fluorimetry. Changes to the melting temperature are screened under various adsorption conditions and used as an indicator of protein destabilization on adsorbent surface. The method was tested for a monoclonal antibody bound to different types of strong cation exchangers at different pH and loading concentrations.

MATERIALS AND METHODS
The monoclonal immunoglobulin mAb07 IgG1 (IP = 8.6, MW = 141.4 kDa, purity > 96%). The adsorption tests were performed on strong IEX resins: Eshmuno CPX (Merc Millipore), Fractogel EMD COO− 650 (M)(Merc Millipore), TOYOPEARL GigaCap S-650M (Tosh Bioscience), Capto S ImpAct (GE Healthcare), POROS™ XS (Life Technologies), TOYOPEARL Sulfate-650 (Tosh Bioscience).

RESULTS
The adsorption equilibrium as well as time dependence of irreversible binding of the protein and aggregate formation was analyzed. The melting temperature data were confronted with adsorption characteristics of the protein. Decrease in the melting temperature was found to be qualitatively correlated with the protein destabilization on the adsorbent surface.

CONCLUSION
We detected destabilization of the protein upon adsorption on all three resin selected for the adsorption-desorption tests (TP GigaCap, S ImpAct, TP Sulfate). The phenomenon of unfolding and mass losses enhanced with adsorption strength and decrease in the loading concentration. The latter was explained by the crowding effect of the protein on the adsorbent surface at its high coverage, which prevented the protein from unfolding. The effect was specific for the resin type, the matrix and the ligand density. TP Sulfate was composed of the same matrix as TP GigaCap but with higher ligand density, which however did not improve the binding capacity for the mAb, instead it made it more prone for unfolding and degradation. The highest stability of the adsorbed protein was observed for S ImpAct having the lowest ligand density and the least hydrophobic matrix.

REFERENCES
SMARTFILMS AND PAPER TABLETS LOADED WITH CAFFEINE: EFFECT OF GRANULATION ON THE CRYSTALLINITY BEHAVIOUR

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INTRODUCTION

Several orally administrated drugs exhibit poor bioavailability due to their inadequate solubility. Recently, smartFilms were introduced as novel oral delivery systems that utilize the pores of ordinary paper as loading sites for therapeutic agents in amorphous state, leading to enhancing the dissolution rate of the loaded drug [1]. Despite its proven effectiveness, such technology is not yet implemented by the pharmaceutical industry, due to the limited flowability of smartFilms in their current state (i.e. pieces of paper). However, such limitation was circumvented via transforming unloaded smartFilms into a free-flowing physical form (i.e. paper granules), which can be compressed into tablets with optimum properties [2]. In the present study, caffeine was selected as a model drug to study the effect of granulation on the crystallinity/amorphous state of drugs loaded within smartFilms pores.

MATERIALS AND METHODS

A paper sheet (Wt. 2.5 g) was cut into small pieces that were loaded with an aqueous solution of caffeine (5 mg/mL). The dried smartFilms were milled and blended with an equivalent amount of sucrose powder (i.e. binding agent) to prepare a w/w paper/sucrose mixture of 20% sucrose content. Then, paper granules were prepared via the wet granulation method with purified water as a granulation liquid. The dried granules were compressed into tablets and their properties were assessed according to the EP requirements. Moreover, crystallinity of caffeine loaded within the paper granules pores was determined by X-ray diffractometer.

RESULTS

Slightly elongated granules were obtained and exhibited good flowability (i.e. angle of repose 30.96°). Caffeine-loaded granules were successfully compressed into tablets that fulfil the EP requirements. Regarding caffeine crystallinity, it was observed that the characteristic peak of caffeine at 2θ = 13.966 disappeared in the X-Ray diffractogram of the caffeine-loaded granules and tablets, in comparison to the corresponding physical mixture, which might indicate that caffeine is loaded within paper granules pores in amorphous state.

CONCLUSION

This study proved that granulation is a reliable approach that can maintain the amorphous state of the drug after being loaded within the pores of smartFilms. Hence, drug-loaded smartFilms can be proposed as promising technology for large scale tablet production.

REFERENCES

ELECTROSPINNING AS A METHOD FOR THE PRODUCTION OF ORODISPERSE FILMS (ODF)

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INTRODUCTION

Oral dispersion films are representatives of a new oral dosage form. This dosage form is suitable for patients with swallowing difficulties (dysphagia), especially the elderly and children. It is also attractive for patients with limited access to drinking water. Solvent casting and hot melt extrusion are most commonly used for their production. Newer electrostatic spinning (electrospinning) technology can achieve the formation of nano/microfiber films. Due to their huge specific surface area, films benefit from faster disintegration. One of the disadvantages is the relatively low dose of API in the film - max 100 mg [1]. At the same time, it is possible to electrospin not only solutions but also suspensions, where the content of the active pharmaceutical ingredient and other solid excipients can exceed the polymer content by several times.

MATERIALS AND METHODS

The films were produced by electrospinning on a Nanospider NS 1WS500U (Elmarco®) from suspension of a polymer matrix containing API. The polymer matrix consisted of water-soluble polymers HPMC and PEO (or PVP), sweetener, flavor, dispersant and solvent system (water:isopropyl alcohol). Tadalafil or meloxicam was used as API. The morphology of the films (SEM Tescan 3), their mechanical and thermal properties (DSC analyse), and dissolution time were investigated.

RESULTS

The films produced by electrospinning had average of fiber diameters in the range of 100-300 nm, with a material thickness of about 300 μm. The film disintegration time is within 5 s, which is well below the ODF limit of 30 s. An important parameter of the film is its mechanical properties, which could be further improved. The DSC results showed no significant difference between the samples laminated at different pressures.

CONCLUSION

Electrospinning is a method suitable for the production of rapidly soluble ODFs. It is possible to electrospin from suspension (in addition, organic solvents for dissolving API can be avoided in this way). The mechanical properties of the ODF will depend on the structure of the film and the choice of suitable polymer(s).

REFERENCES

DISSOLUTION ASSESSMENT OF ORAL LOCALLY ACTING PEPTIDE DRUG PRODUCT

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INTRODUCTION

Linaclotide (LIN) is a 14-amino acid, guanylate cyclase C (GC-C) receptor agonist structurally related to the endogenous guanylinpeptide family. Activation of the GC-C receptor increases gastrointestinal (GI) secretion and transit. Linaclotide was approved in 2012 for the treatment of chronic idiopathic constipation (CIC) and constipation-predominate irritable bowel syndrome (IBS-C) in adults. In vitro digestion studies showed that, as a peptide, linaclotide was susceptible to degradation by intestinal fluids. Moreover, neither parent drug nor its metabolite is detectable in blood plasma [1]. One of the options for demonstrating bioequivalence (BE) of linaclotide generic drug product is based solely on a comparative in vitro dissolution testing [2]. Thus, the purpose of the study was to develop a validated RP-HPLC-UV method and conduct multi-point, multi-media dissolution testing using USP 2 and USP 4 apparatuses for reference listed drug (Constella 290μg).

MATERIALS AND METHODS

Linaclotide (98.2% pure) was purchased from Ontores Biotechnologies (Zhejiang, China). Constella 290μg hard gelatine capsules were purchased from a local pharmacy. Shimadzu LC-2030C Plus (Kyoto, Japan) equipped with a UV detector was used for HPLC analysis. The chromatographic separation was performed on a Luna Omega Polar C18 1.6 μm 100Å, 50 × 2.1 mm column (Phenomenex Ins., CA, USA) with injection volume of 100 μL. Dissolution testing of Constella 290μg capsules was performed applying USP 2 and USP 4 apparatuses (both from SOTAX, Aesch, Switzerland) in a set of compendial (pH: 1.2, 2.0, 4.5 and 6.8) and biorelevant (SGFsp pH 1.2, FaSSGF pH 1.6, FaSSIF pH 6.5) media.

RESULTS

Two RP-HPLC-UV methods were developed and validated: the isocratic method for linaclotide quantification in compendial dissolution media and gradient method for assays in biorelevant media. The fastest dissolution kinetics of LIN was demonstrated in HCl solutions with a pH range of 1.2-2.0, slightly slower in 0.05M phosphate buffer pH 6.8, and the slowest in 0.05M acetate buffer pH 4.5 (f2 < 50). We observed the similarity of LIN dissolution profiles (f2 > 50) in biorelevant media (FaSSGF vs. FaSSIF).

CONCLUSION

Constella 290μg product exhibits very rapid (> 85% within 15 min using USP 2 apparatus) or similarly rapid (> 85% within 30 min using USP 4 apparatus) in vitro dissolution characteristics.

REFERENCES

INTRODUCTION

The goal of the study was to assess the biopharmaceutical properties for selected immediate-release (IR) solid oral formulations containing ibuprofen (IBU) with a dose 400 mg (Ibum Express, Ibuprom Max, Ibuprom RR), 684 mg of IBU lysine salt (LizyMAX) and 512 mg of IBU sodium dihydrate (Nurofen Mięśnie i Stawy Forte) using biorelevant dissolution testing methods simulating in vivo conditions.

MATERIALS AND METHODS

The UV spectrophotometric method with detection at the wavelength of 264 nm – 284 nm was developed and validated for dissolved API quantification in the dissolution media. The disintegration time of all products was tested in 10 mM HCl solution. Dissolution studies were performed according to the USP monograph for IBU IR tablets using paddle apparatus and standard pharmacopeial as well as biorelevant media (simulated physiological fluids of low ionic strength, i.e., to 5 mM PB pH 6.8, Hanks’ buffer stabilized with 5mM PB pH 6.8 or with the pHysio-grad® device).

RESULTS

It was found that all tested formulations meet the pharmacopeial requirements for IR tablets and capsules (disintegration and dissolution in 50 mM phosphate buffer (PB) pH 7.2). Nevertheless, we observed differences in the disintegration time of the tested products (from about 2 min. to 11 min.). The highest IBU dissolution rate (k) in 50 mM PB pH 7.2 and 6.8 was obtained for Ibuprom RR (k~0.270 min⁻¹) and the lowest for Nurofen Mięśnie i Stawy Forte (k~0.025 min⁻¹). It has been shown that in biorelevant media the fastest dissolution rate was observed for products with IBU salts (LizyMAX>Nurofen Mięśnie i Stawy Forte) and the slowest for Ibuprom Max (IBU free acid).

CONCLUSION

The dissolution rate of IBU from the tested products in biorelevant media correlates well with the rate of API absorption in vivo (data taken form the literature [1]). Also, the dissolution rate of IBU from the solid oral dosage IR formulations studied depends to the greatest extent on its chemical form in the given product, and then on the excipients that affect the disintegration and dissolution of the API.

REFERENCES

IMPACT OF LIQUID EXCIPIENTS ON ADHESIVE PROPERTIES OF PDMS AND POLYACRYLATE TRANSDERMAL DELIVERY SYSTEMS

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INTRODUCTION

PSA (pressure-sensitive adhesives) are adhesive polymers widely used in transdermal delivery systems (TDS). Most common PSAs are polyacrylates and polydimethylsiloxanes (PDMS). Liquid additives, such as propylene glycol or triacetin, that can be used i.e. as co-solvents or permeation enhancers, are known to modify the adhesive properties of PSAs, which can be attributed to plasticizing/antiplasticizing effect [1]. Various methods of evaluation of the adhesive properties in vitro are described in the literature [2]. The following work is aimed to investigate the adhesive properties of polyacrylate and PDMS matrices with or without liquid additive.

MATERIALS AND METHODS

Investigated TDS (placebo) were prepared by casting and solvent evaporation. Two commercially available polyacrylates (DuroTAK 87-2852 and 87-4098, Henkel, Brussels, Belgium) and two PDMS (BioPSA MD 7-4502 and SSA MG 7-9850, Dow Corning, Wiesbaden, Germany) were used to form the adhesive matrices. The investigated liquid excipients were: PEG 400, propylene glycol, isopropyl myristate, triacetin, triethyl citrate and low viscosity silicone oil. Evaluation of adhesive properties was performed by probe tack test, as well as by a 90° peel adhesion test (with metal surface as substrate), using TA.XT Plus texture analyser (Stable Micro Systems, Godalming, UK).

RESULTS

Addition of liquid excipients (10%) caused significant decrease in adhesion force (tackiness) in all A1 formulations (with DuroTAK 87-2852), while in A2 (with DuroTAK 87-4098) significant decrease was noted only in formulations with silicone oil and PEG. The work of adhesion was increased in several formulations. In the probe tack test of PDMS formulations, both force and work of adhesion were reduced. In 90° peel test no significant reduction in adhesion force was noted in acrylate formulations. Moreover, in A2-MIP and A2-GP, the adhesion force was noticeably improved.

CONCLUSION

Liquid excipients impact the adhesive properties of patches, which can be utilized to purposely modify the formulation properties. The described work allowed to detect possible incompatibilities in formulations of TDS. The results indicate that described test methods lead to different conclusions and are not equivalent in terms of assessment of adhesiveness.

ACKNOWLEDGEMENTS

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REFERENCES

INTRODUCTION

Polymeric micelles are one of the novel nano-drug delivery systems, with many advantageous properties, most importantly the ability to encapsulate a drug with poor water solubility thereby solubilizing it and increasing its bioavailability. Intranasally administered polymeric micelles tend to follow the axonal pathways delivering drugs to the central nervous system via “nose-to-brain” direct route bypassing the blood-brain-barrier [1].

MATERIALS AND METHODS

The film-method was used to formulate meloxicam (MEL)-loaded Soluplus® polymeric micelles optimized by Box-Behnken factorial design. Particle size and distribution were measured using DLS method. The morphology study was executed via TEM. Thermodynamic solubility and encapsulation efficiency were quantitatively measured using HPLC. Surface free energy and polarity were also determined. For characterization of MEL-Soluplus® interactions in solid state, various methods were used: XRPD, thermal analysis and vibrational spectroscopy. After freeze-drying, the physical stability was tested for 12 months at 5°C ± 3°C. In vitro dissolution and nasal diffusion tests were evaluated in order to test the products for the requirements of intranasal administration.

RESULTS

The precipitated polymeric micelles were easily dissolved in water unlike the original material. The particle size and distribution of the spherical nanoparticles were decent with high encapsulation efficiency, solubility and polarity. The material structure investigations showed that a new material was formed which differs from both the polymer and the model drug. In vitro studies showed fast drug release and high nasal diffusion of the formulation. The physical stability was pleasing.

CONCLUSION

We conclude that Soluplus® is a good excipient for the preparation of polymeric micelles. Formulation of polymeric micelles can improve the solubility of poorly soluble agents, which can be useful for developing “value added” preparations.

REFERENCES


The work was supported by the National Research, Development and Innovation Office, Hungary (GINOP-2.3.2-15-2016-00060) and the Gedeon Richter Plc. Centennial Foundation (Gyömrői 19-21, Budapest, H-1103, HU).
EFFECT OF ACTIVE INGREDIENTS ON VISCOSITY OF ALGINATE SOLUTIONS

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INTRODUCTION

Alginates are natural polymers used as stabilizers, thickeners and gelling agents in many fields such as pharmaceutical, cosmetic and food industry [1]. In pharmaceutical and cosmetic technology, alginates can be utilized as viscosity-enhancing and gelling agents for topical preparations. The present study aims on determining whether the addition of different additives (intended for use for self-tanning effect) affects the properties of alginate solution.

MATERIALS AND METHODS

Three substances which can be used in composition of a topical preparations as self-tanning dermatological formulation (arginine, glycine and dihydroxyacetone - DHA) have been chosen to this study. Polymer solutions were obtained by dissolving sodium alginate (Sigma-Aldrich, St. Louis, MO, USA) in pH 7 phosphate buffer. Solutions were prepared as “placebo” and with addition of the active ingredients (Arginine, Glycine, Dihydroxyacetone – Sigma-Aldrich, St. Louis, MO, USA). The viscosity measurements were conducted for solutions containing various concentrations (0.3-1.4% w/w) of polymer, and fixed concentrations of additives (2% aminoacids, 5% DHA). The viscosity of the solutions was measured with DHR3 Rheometer (TA Instruments, Cheshire, UK) using a cone-plate geometry [2]. A critical overlap concentration (C*) of alginate was determined for each investigated system and used as a differentiating parameter.

RESULTS

It was found that in the studied concentrations of the polymer and additional substances there is no significant differences between relative viscosities of solutions. The C* was determined to be around 1% regardless of the substance added to alginate solution. Such results confirm no interaction between polymer and investigated additives.

CONCLUSION

The investigation using method described above allows to detect possible interactions between polymer and additives in solution. It is a crucial step in development of liquid and semi-solid preparations. The obtained results, indicating no impact of tested aminoacids and DHA on alginate solutions allow for follow-up investigation of alginate-based systems.

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DETERMINATION OF MERCURY IN TOPICAL PRODUCTS AND EVALUATION OF POTENTIAL RISKS

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INTRODUCTION

Mercury is not allowed in any other cosmetic product except in a trace amount of less than 1 ppm and only if its presence is unavoidable under good manufacturing practice. Even with quantities of mercury less than the maximum value admitted by law, summing up the quantity of all the products used per day, we reach quantities of toxic exposure. The main goal of our research is to demonstrate that a regular cosmetic or hygiene product (without lightening effects) application raises the risk of mercury accumulation in the body and could produce toxic side effects.

MATERIALS AND METHODS

Mercury was determined from 42 samples (face creams, hand creams, body lotions, foot creams, and toothpaste). They were weighed and analyzed using the AMA 254 atomic absorption spectrometer. A wavelength of 253.65 nm is used as a light source, emitted by a low-pressure mercury vapor lamp resulting in the detection limit of 0.00001 μg Hg. This method uses the radiation absorption phenomenon by free mercury atoms in a basic state. It consists in the fact that free mercury atoms absorb the radiation emitted by the mercury lamp, the hollow cathode of which is made of mercury. As a result, the initial intensity of radiation emitted by the mercury lamp is reduced, and it is recorded by the spectrometer. The magnitude of this reduction is proportional to the number of mercury atoms in released pairs of this element.

RESULTS

After we calculated the average daily weight of each product, we multiplied that value with the average intake of mercury in ng per day and adding up to 126.6 ng of daily mercury intake from cosmetic products. Considering the amount of mercury measured in cosmetic products, and a half-life of 50 days for mercury metabolism, we estimate an amount of 3.242 μg of mercury reaching our bodies per month, approximately double than the amount consumed through drinking water but way less than that brought in by fish and food consumption. Theoretically, all these cosmetics bring a lower intake of Hg compared to other sources, such as food. Considering the 126.6 ng Hg/day, with a half-life of 50 days and assuming linear decay, using the formula: rate of decay=daily intakedose×(12/days after intakehalf time we approximate it requires 56 days of average usage for mercury to reach the alert level of 5 μg, and over the span of a year, more than 9 μg of Hg might be accumulated in our bodies. In our calculation, we took the conservative half-time of 50 days, but it is important to note that studies have found half-times of up to 150 days, case in which the results would be much higher. The alert level of mercury in the human body is 5 μg, while at over 20 μg we...
could start to see the side effects. Practically, using common creams for 30 days brings in an amount of 3.242 μg, which is 16% of the level of mercury required to cause visible side effects, while over the span of a year, average usage of cosmetics amounts to 9 μg of Hg, or 45% of the amount required to cause visible side effects.

**CONCLUSION**

5 μg of mercury in our body is the alert level for this heavy metal, and while side effects do not develop until the level of 20 μg is reached, the 2% intake that cosmetics are responsible for could represent the “tip of the iceberg” in an already saturated and sensitive mercury metabolism, especially in people with a diet rich in fish and meat. Through this study, we want to trigger an alarm regarding the amount of daily mercury exposure by applying cosmetics.

**REFERENCES**

LACTOFERRIN BASED CAPSULES PREPARED BY FLUID-BED COATING METHOD

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INTRODUCTION

Nowadays, there are orientations towards the circular economy in many areas with the aim of ensuring a zero-waste industry. Whey is a co-product in milk processing, and it was considered as a waste material for many years. However, due to its rich composition with emphasis on proteins, it represents a valuable material in many fields. One of the most interesting proteins is lactoferrin (Lf), which expresses several beneficial effects on human health [1].

MATERIALS AND METHODS

The first coating layer was prepared from solution of Lf, HPMC and PEG 6000, while the second coating layer was enteric, composed of Eudragit L30-D55. Such coatings were applied to the Cellets 200 by utilizing Wurster chamber, and coated pellets were filled into the hard gelatine capsules. Final product and intermediates were characterized using reversed-phase HPLC, TGA, DSC, Mastersizer 3000 and other techniques.

RESULTS By varying process parameters and formulation composition capsules with Lf protected from gastric enzymes and low pH environment were obtained. They are intended for targeted local delivery to the small intestine, while expressing selective growth inhibition of pathogenic microorganisms. Despite high mechanical stress during processing, the instability of Lf was not detected. Obtained capsules can be used as a dietary supplement, preventing gastrointestinal distress as a promising alternative for typically used antibiotics or activated carbon, for example in case of travellers with sensitive gut.

CONCLUSION

In the present study we demonstrated that the selection of the appropriate process parameters along with the suitable whey composition enables preparation of gastro-resistant capsules with Lf in a dose of 200 mg with insignificant impact of Lf stability.

REFERENCES

CHARACTERIZATION OF RHEOLOGICAL PROPERTIES OF POLYMERS WITH RESPECT TO COLON-TARGETED DELIVERY OF LIQUISOLID TABLETS

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INTRODUCTION

Preparation of liquisolid systems (LSS) is a novel concept for controlled drug release in colon-targeted drug delivery systems. Combination of traditional matrix tablets with LSS allows to optimize therapy of colonic ailments with poorly soluble drugs. Thus, this pre-formulation study aims at rational selection of retarding agent for further preparation of colon-targeted LSS based on analysis of polymers mainly by rheological measurements.

MATERIALS AND METHODS

Dispersions of polymers (Hydroxypropyl methylcellulose, K4M and K15M; carboxymethylcellulose sodium, CMC; Guar gum, GG) simulating gel layer formed around matrix tablet upon hydration in the gastrointestinal tract were prepared in biorelevant dissolution media Fasted State Simulated Gastric/Intestinal/Colon Fluid (FaSSGF/ FaSSIF/FaSSCoF). Rheological measurements were performed on a rotational rheometer (Malvern Kinexus) at 37o C and shear rate 0.01-100 s-1. Power law model was used to fit flow curves and describe rheological behaviour of tested polymers.

RESULTS

As expected, shear thinning behavior was observed for all polymers. The degree of shear thinning was lower for K4M in all biorelevant media and for GG in media with higher pH (FaSSIF and FaSSCoF). Viscosity of the polymers decreased quickly upon dilution, apart from GG. Slower decrease in GG viscosity upon dilution can be correlated with a slower loss of gel layer formed around the tablet and hence more prolonged drug release. However, distinct pH-dependent viscosity was noted for GG. Thus, GG can be expected to show fluctuations in terms of controlled release, as pH may differ in inflamed intestine [1]. Contrarily, the effect of pH was minimal in the case of K15M, K4M and CMC.

CONCLUSION

Based on the results, a logical approach could be to combine guar gum with any of the other tested polymers (K4M, K15M or CMC) in order to minimize pH influence and dilution effect. Nonetheless, further experiments are required for selection of suitable polymer(s), as other properties (e.g. mucoadhesion) will also play a significant role during the drug release.

REFERENCES


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PRODUCTION OF POLYPROPYLEN NANOPLASTICS AND THEIR EFFECTS ON VIBRIO FISHERI

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INTRODUCTION

Plastic pollution appears to be one of the biggest challenges of our century but detailed information about its environmental and acute toxicity is not yet available [1,2]. One reason is the limited availability of standardized nanoplastic in research that allows for systematic studies in this regard. Therefore, this study aimed at developing a method for the production of nanoplastics for systematic toxicity testing.

MATERIALS AND METHODS

Pellets of the thermoplastic polypropylene (PP) were frozen at -20 °C, and dry milled to gain microsized PP particles. Subsequently, small scale bead milling using 1 % (w/w) microplastic in purified water was performed at 1,200 rpm and room temperature for up to 6 days. Samples were filtered with a 200 nm membrane filter and characterized regarding their size and zetapotential. In addition, preliminary toxicity studies to assess the aqueous toxicity of the nanoplastic were performed. For this, different quantities of PP-nanoplastic were added to precultured *Vibrio fischeri* in artificial sea water and the bio-luminescence, which surrogates the viability of the bacteria, was determined after 15h.

RESULTS

Milling of PP was very ineffective, and nanoparticles were obtained only after extremely long milling times (up to several days). The results indicate that also in the oceans the transfer of larger sized plastic waste into nanoplastic might be slow. Hence, there would be sufficient time to collect plastic wastes before it turns into toxic nanoplastic. The pp-nanoparticles in this study - after 6 days of milling - possessed a particle size of 113 ± 1 nm, a polydispersity index of 0.15 and a ZP of -37.9 ± 2.5 mV. Toxicity studies revealed a pronounced decrease in bio-luminescence of *Vibrio fischeri*, providing first evidence of the immense aqueous toxicity of PP-nanoplastic.

CONCLUSION

A method for the production of nanoplastic and a model for the assessment of its aqueous toxicity were developed in this study as base for more detailed studies on the toxicological profile of nanoplastic.

REFERENCES

A METHOD FOR TIME AND SPACE RESOLVED DETERMINATION OF THE DERMAL PENETRATION EFFICACY OF BETA-CAROTENE

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INTRODUCTION

Beta-Carotene (pro-vitamin A) possesses various pharmacological properties, making it highly interesting for dermal application. Depending on its intended use, dermal or transdermal penetration with fast and/or prolonged action might be desired. Therefore, formulations with tailor-made penetration profiles need to be developed. A pre-requisite for this is the availability of test methods that allow for a time and space resolved determination of the dermal penetration of the active compound. Such a method was recently developed for curcumin [1]. The aim of this study was to investigate if the method can also be used for other natural active compounds, e.g., beta-carotene.

MATERIALS AND METHODS

Beta-carotene was incorporated in an o/w cream base and was applied on fresh porcine ears in finite dose setups (1 mg/cm² and 2 mg/cm²) that were allowed to penetrate the skin at 32 °C for 2 h and 4 h. Afterwards, punch biopsies were taken that were cryo-sectionized and imaged with inverted epifluorescence microscopy. Subsequently, the images were subjected to digital images analysis (DIA) with ImageJ software to assess the total amount of penetrated beta-carotene (TAP), its mean penetration depth (MPD) and the stratum corneum thickness of the skin (SCT). Results were compared to untreated skin and to skin treated with the cream vehicle without beta-carotene.

RESULTS

Application of 1 mg/cm² and penetration for 2 h resulted in a TAP of 3.0 MGV/px. The MPD was 27 μm, indicating that carotene penetrated into the stratum corneum but not deeper. Application of 2 mg/cm² doubled the TAP but the MPD was similar. An increase in penetration time to 4 h resulted in a pronounced transdermal penetration of beta-carotene and increased the TAP to 213 % for the 1 mg/cm² doses and to 240 % for the 2 mg/cm².

CONCLUSION

The porcine ear skin model with subsequent DIA allows for a detailed time and space resolved determination of the dermal penetration efficacy of beta-carotene and thus represents the base for the development of dermal beta-carotene formulations with tailor-made penetration profiles.

REFERENCES

STABILIZATION OF ROSUVASTATIN CALCIUM WITH CALCIUM PHOSPHATE EXCIPIENTS

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INTRODUCTION

Rosuvastatin calcium (RSC) is a synthetic drug, which is commonly used to treat and prevent cardiovascular and coronary heart diseases. Like other statins it is challenging to be formulated into stable dosage form due to its susceptibility to degradation. Various strategies have been proposed to overcome this issue, and the most popular seems to be the use of excipients such as inorganic salts of multivalent metals as stabilizing agents. The presence of multivalent inorganic cations suppresses susceptibility of RSC to oxidative degradation and lactonization.¹,²

MATERIALS AND METHODS

RSC from Cadchem Laboratories Limited (Chandigarh, India) was mixed with selected excipients in a weight ratio of 1:1, and the obtained mixtures were placed in glass vials with plastic lids. The samples were stored in an HPP 750 stability chamber (Memmert, Büchenbach, Germany) under stress conditions (50°C/80% RH) for 80 days and analysed for impurity content by HPLC method. Excipients chosen for this study included fillers/diluents used in direct compression processes such as α-lactose monohydrate (Tablettose® 100), microcrystalline cellulose (Heweten® 102), anhydrous dibasic calcium phosphate (DI-CAFOS® A150), anhydrous dibasic calcium phosphate neutral (development product), and tribasic calcium phosphate (TRI-CAFOS® 500), as well as glidants such as fumed silica (Aerosil® 200) and tribasic calcium phosphate (TRI-CAFOS® 200-7).

RESULTS

RSC itself was not stable under stress conditions. The presence of the excipient in the binary mixtures affected the rate of increase in the impurity content of the test samples. Mixtures with lactose monohydrate and colloidal silica were the least stable. The best stabilizing effect was observed for both tribasic calcium phosphates as well as for anhydrous dibasic calcium phosphate neutral. In the presence of anhydrous dibasic calcium phosphate of acidic pH as well as microcrystalline cellulose, RSC was found to be less stable.

CONCLUSION

The use of pH-neutral calcium phosphate excipients allows stabilisation of RSC and subsequent production of tablets by direct compression. The stabilising effect of tribasic calcium phosphates is stronger than that of dibasic calcium phosphates.

REFERENCES

IN VIVO ANTITUMOR EFFECT OF RESVERATROL NANOCRYSTALS IN MICE AFTER INTRAPERITONEAL INJECTION

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INTRODUCTION

Resveratrol (3,5,4′-trihydroxy-stilbene) is a potential antitumor compound because of its antioxidative, anti-inflammatory, anti-angiogensics and anti-proliferation characteristics [1]. Due to poor solubility and bioavailability, its potential therapeutic use is very limited [2]. The aim of this research was to investigate effects of resveratrol nanocrystals on fast-growing and angiogenesis-dependent Ehrlich ascites tumour (EAT) in mice. Furthermore, we investigate the relationship between liver and kidney damage levels through histological analysis of the presence of cells in mitosis, apoptosis and necrosis.

MATERIALS AND METHODS

The tumour was caused by intraperitoneal (IP) injection of 2.5 x 10⁶ cells into the abdominal cavity of Swiss albino mice [3]. Treatment of animals with EAT tumour in groups was started the next day by IP injection of resveratrol or resveratrol nanocrystals at dose of 25 mg/kg every other day for 14 days. Animals were sacrificed on the 15th day and organs of interest were collected for further analyses.

RESULTS

The results indicate that resveratrol nanocrystals have an inhibitory effect on tumour cell growth, but also can induce acute toxicity of the kidney and liver. Microscopic analysis of the number of blood vessels in the peritoneal sheath confirms the great angio-suppressive potential of resveratrol nanocrystals, which in turn leads to inhibition of tumour growth.

CONCLUSION

Resveratrol nanocrystals have shown very promising results as an anti-cancer agent, but the mechanisms of toxicity needs to be further clarified.

REFERENCES

ANALYTICAL CENTRIFUGATION: A NOVEL WAY FOR PARTICLE SIZE ANALYSIS?
– A COMPARISON

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INTRODUCTION

Physiochemical characterization plays an important role for the development of nanoformulations because properties such as the particle size distribution can influence the biopharmaceutical parameters depending upon the route of application. Commonly used methods for the analysis of particle sizes are dynamic light scattering (DLS) and light microscopy (LM) [1]. An analytical centrifuge (LUMiSizer) was used as new technique for particle size analysis (PSA), and compared to the common methods for particle size analysis (PSA): DLS and LM. In this study, a two-phase fat emulsion was used as model system for PSA and different concentrations of PBS buffer were added to influence the behaviour of the emulsion in terms of stability, surface charge and mobility.

MATERIALS AND METHODS

Lipofundin® MCT 20% was utilized as two-phase model system. To produce the PBS buffer purified water, NaCl, KCl, Na2HPO4 and KH2PO4 were used. PBS buffer was added in different concentrations (in ten steps from 1X to 0) to Lipofundin®. Size characterization was performed by three different techniques DLS, LM and an analytical centrifuge (LUMiSizer, LUM, Berlin, Germany).

RESULTS

The results of the used methods showed quite different trends. The PSA by DLS revealed droplet sizes in a range between 265 and 280 nm without influence of PBS buffer concentration. On contrary, LM showed that there was an increase of larger oil droplets in a range of 5 to 20 μm with higher PBS buffer concentration. Hence, DLS could not securely detect the instability caused by the addition of the electrolytes. With analytical centrifugation, droplet sizes up to 500 nm were determined. The results showed that there was a slight increase of droplet size with higher electrolyte concentration. However, also this method was unable to detect the micrometre-sized particles, found by light microscopy.

CONCLUSION

This study showed that an analytical centrifuge for PSA can be a useful in addition to the commonly used methods DLS and LM. A broad spectrum of particle sizes from a few nanometres up to several micrometres can be detected with LUMiSizer without neglecting the minority populations of smaller or larger particles. Limitations are too high sedimentation/floating velocities of large particles.

REFERENCES

INTRODUCTION

Endogenously expressed microRNAs (miRNAs) represent regulators of gene expression at post-transcriptional levels of numerous (patho)physiological processes. As miRNA dysregulation is often associated with the development and progression of various diseases, miRNA-based therapy could provide a valuable strategy for the treatment or prevention of genetic, immunological, or metabolic disorders. Although miR-27a has been identified as a promising candidate for miRNA mimic therapy of obesity, its application is limited due to the enzymatic degradation and low membrane permeation. To overcome these problems, we developed cationic lipid nanoemulsion (CNE) as a non-viral carrier for miR-27a.

MATERIALS AND METHODS

Briefly, CNE containing 0.05% of stearylamine as cationic lipid, 4.95% of Miglyol® 812, 1% of Tween 80, and 1% of Poloxamer 188 were produced using a hot high-pressure homogenization operating on 800 bar and five cycles at 70°C. The following physicochemical properties of CNE were determined: droplet size, polydispersity index (PDI), zeta potential (ZP), viscosity, and pH value. In addition, we investigated how different mass ratios of CNE and miR-27a (1:5, 1:2.5, 1:1, 2.5:1, 5:1, 10:1) influence the physicochemical properties of the formed complex.

RESULTS

The CNE had a mean diameter of 109.8 ± 0.06 nm (PDI of 0.155 ± 0.01) and a ZP value of +55.43 ± 0.57 mV, while pH and viscosity were 8.69 ± 0.08 and 1.48 ± 0.07 mPas, retrospectively. Complexation of CNE with different mass ratios of miRNA revealed that there were no significant differences in particle size of the complexes (around 140 nm) over the mass ratio of 2.5:1. The biggest particle size was observed in a 1:1 ratio (729.03 ± 93.51 nm) due to low ZP values (around 0 mV). However, the ZP value progressively increased from -9.85 ± 0.64 mV to +56.84 ± 1.27 mV with the increase of the CNE:miRNA ratio from 1:5 to 10:1, identifying the CNE:miR-27a complex (5:1) as the leading formulation.

CONCLUSION

Our investigations suggest that CNE poses a high potential to be a non-viral gene carrier, which could be used in miRNA replacement therapy in metabolic diseases, such as obesity.

REFERENCES

EFFECT OF STEAM STERILIZATION ON THE GEOMETRIC PROPERTIES OF 3D PRINTED MICRONEEDLE ARRAY

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INTRODUCTION

Before the final usage of the proposed 3D printed microneedles (MNs) as physical enhancers of transdermal drug delivery, it is necessary to perform process of their sterilisation. Unlike conventional transdermal delivery systems, MNs pierce the outermost skin layer and penetrate the epidermis and dermis, which are considered sterile body parts [1]. During one of the most common sterilization processes – the steam sterilization, the temperatures around 135°C and steam pressure around 0.2 MPa are achieved. This thermal load can deform the shape and change the dimensions of MNs. Therefore, we have investigated the effect of thermal load on the change in shape and dimension of 3D printed MNs.

MATERIALS AND METHODS

MNs were designed using CAD software and printed with BioMed Amber resin (Formlabs, UK) using a Form 3B printer (Formlabs, UK). MNs were arranged in 6 rows and 6 columns on a 10 × 10 mm baseplate. After the end of the printing process, MN arrays were peeled off carefully from the building platform and rinsed in isopropyl alcohol to remove any unsolidified resin and cured in a UV-A heated chamber (Formlabs, UK). Afterward, MNs were sterilized at 135°C for 30 minutes under steam pressure of 0.2 MPa using autoclave (MELatronic 23, Germany). The actual shape and height of the MNs were analyzed and measured by microscope Mitutoyo TM-505 (Kanagawa, Japan) before and after sterilization to consider potential changes in MNs shape and dimensions under thermal load during the sterilisation.

RESULTS

Investigations performed show no significant change on the shape of MNs. The heights of MNs before sterilization were in the range of 700 ± 50 μm. As consequence of the thermal load during the steam sterilization, the heights of MNs have decreased and amounted in the range of 650 ± 50 μm.

CONCLUSION

Steam sterilization did not cause appreciable deformations, nor significant changes in the dimensions of MN arrays. Therefore, the next phase of our investigations will include effects of the steam sterilization into the mechanical properties and the skin penetration tests.

REFERENCE

INFLUENCE OF CHOICE OF METHOD AND TEST CONDITION ON THE RESULTS OF DRUG RELEASE STUDY FROM LIPID MICROSPHERES

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INTRODUCTION

Testing the release of a drug substance from a dosage form is a commonly used technique not only in research and development laboratories but also in quality control. In studies of modern dosage forms, such as solid lipid microparticles (SLM) dispersions, the usefulness of classical compendial methods is usually limited [1, 2].

Therefore, the aim of the conducted research was to compare three non-pharmacopoeial methods of testing the drug release and the influence of various factors (e.g. the type of dialysis membrane) on the obtained results.

MATERIALS AND METHODS

SLM (a few micrometers in diameter) dispersions with Compritol, containing two model substances – cyclosporine or indomethacin, were prepared and their physicochemical properties were characterized [2]. In the next stage of the research in vitro drug release profiles obtained in different set up of the test were compared. The release study was performed using three methods: a) in the system without a membrane (dispersion of microspheres in the acceptor fluid), and in systems with a semi-permeable membrane: b) in a dialysis bag and c) in a horizontal diffusion chambers (side-by-side). The influence of the type of dialysis membrane and acceptor fluid on the obtained results was also assessed.

RESULTS

It has been shown that the release study from SLM formulations conducted with different methods lead to substantially different results. On the basis of the performed experiments, the dialysis bag method (b) was found to be the most advantageous, as well as the use of the method without a membrane (a).

CONCLUSION

The choice of the method to study drug release from SLM should be preceded by preliminary experiments, and all comparative tests should always be carried out using the same method and exactly the same test conditions.

REFERENCES

INTRODUCTION

Liquid antisolvent precipitation (LASP) is one of techniques used for micronization and nanonization of poorly soluble APIs with the aim to improve their dissolution rate, which in consequence enhances their bioavailability [1]. Applying ultrasound (US) during or directly after this process may lead to further reduction in particle size [2]. The aim of this work was to optimize LASP+US processing parameters in order to produce nanosized particles of BCS class II drug cilostazol (CIL), and to characterize the resulting nanosuspension.

MATERIALS AND METHODS

Solvent and stabilizers were selected in screening studies. LASP process variables (stabilizer amount, stirring speed, feed concentration) were optimized using Design of Experiments (DoE) to identify the settings resulting in the smallest achievable particle size distribution (PSD). Subsequently the effect of sonication on further possible reduction was investigated. The influence of US parameters (amplitude, time, feed concentration) was evaluated with DoE and LASP+sonication was optimized to yield nanosuspension. The material was characterized for PSD (laser diffractometry), solid state analysis (DSC, XRPD, FTIR), morphology (SEM, AFM), as well as solubility and dissolution rate (USP 2 apparatus).

RESULTS

CIL obtained with optimized LASP process alone was in the form of microparticles (d90 = 8.39 μm). Optimal parameter settings were identified for smallest achievable microparticles for further reduction, i.e. DMSO/water 10/90, stirring 600 rpm and PVA as nanosuspension stabilizer at 1:1 weight ratio to cilostazol. Critical sonication parameters were revealed as feed concentration and US energy. Owing to final optimization, nanosuspension with d50 value of ~300-400 nm and d90 below 1.5 μm was produced by 1 hour of probe sonication at 100% amplitude. Both micro- and nanoparticles retained original polymorphic form A, but displayed slightly changed crystal habit. The advantage of nanonization over micronization for dissolution rate enhancement was confirmed.

CONCLUSION

Antisolvent precipitation combined with sonication was demonstrated to be successful in production of poorly soluble cilostazol’s nanosuspension with enhanced dissolution while retaining the original solid state characteristics.

REFERENCES

EFFECT OF CHITOSAN-BASED CARRIER ON ANTI-HERPES ACTIVITY AND MICROBICIDE PENETRATION CHARACTERISTIC THROUGH HUMAN VAGINAL MUCOSA

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INTRODUCTION

Vaginal microbicide delivery systems are promising concept to prevent from sexually transmitted viral STV infections. Much attention has been paid toward smart polymers (e.g. chitosan) with adjunctive pharmacological activity to improve the efficacy of conventional drugs. We have previously shown that spray-dried microbeads (MB) with chitosan glutamate (gCS) hold promise as mucoadhesive vaginal delivery platform for model antiviral agent zidovudine (ZVD) (1). The goal was to evaluate penetration characteristic and to examine in vitro antiherpes effect of chitosan-based microbeads.

MATERIALS AND METHODS

Penetration studies were conducted in flow-through teflon diffusion chambers (compatible with Bronaugh cells) using human vaginal epithelium obtained (bioethical permission no R-I-002/462/2018). In vitro activity of formulations toward HSV-2 infection was determined by viral attachment assay in human keratinocytes HaCaT and human vaginal epithelial cells VK2-E6/E7 and analyzed by plaque forming test (2).

RESULTS

Alterations in penetration behaviour were observed among formulations differed in gCS to ZVD ratio and the presence of higher amount of gCS in microbeads increased the drug flux at the initial stage of studies. Microbeads were found to impact HSV-2 infectivity by inhibition of viral attachment and the rate of reduction in HSV-2 plaque size was about 50% in tested cell lines.

CONCLUSION

The obtained results demonstrated a potential of gCS as antiherpes adjunctive and penetration enhancer of microbicide through vaginal mucosa but further more detailed studies are needed to elaborate the mode of antiviral effect.

REFERENCES

CHARACTERIZATION OF ITRACONAZOL ELECTROSPUN FIBROUS SHEETS

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INTRODUCTION

Itraconazole (ITZ) is a poorly water soluble weak base and a potent antifungal drug, used both in dermal and systemic fungal infections [1]. Polymer based solid dispersion, like electrospun nanofibers increase specific surface, thus enhance solubility [2]. ITZ loaded electrospun fibrous sheets were prepared in order to improve API solubility.

MATERIALS AND METHODS

Itraconazole (Acros) was incorporated in polyvinylpyrrolidone - PVP (Plasdone K29/32, ISP Technologies) based fibres. ITR stock solutions were prepared in alcohol – DCM mixture. Electrospinning was applied using the following parameters: 10 cm collector needle distance, 20kV voltage, flow rate of 8ml/min with an eSpin Tube apparatus. Morphology of the fibres (SEM), drug load and comparative dissolution was investigated. DSC and FTIR studies were also conducted.

RESULTS

SEM investigations indicated that fibre diameter is in nanosize range. Drug content was 33.21±0.9 %. Dissolution studies implied comparison with pure drug and a commercially available tablet formulation. Fibres present superior dissolution.

FTIR spectra of fibres show widening and merging of expected characteristic peaks. DSC curves show the crystalline to amorphous transition of ITR due to fibre formation (lack of the sharp melting endotherm at 165oC).

CONCLUSION

ITZ loaded electrospun nanofibers showed an almost complete dissolution of the API proving an improved solubility.

REFERENCES


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A NOVEL IN VITRO METHOD FOR THE ASSESSMENT OF THE DERMAL PENETRATION KINETICS OF CHEMICAL COMPOUNDS BY USING FLUORESCENCE SPECTROSCOPY

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INTRODUCTION

Interest in topical and transdermal products is increasing worldwide especially for the innovative nanosuspension in cosmetic and pharmaceutical fields. Various methods are used for the evaluation of dermal drug penetration. Franz diffusion is classified as a gold standard to study the release behaviour of dermal formulation, but it has many limitations like difficult set up, the application needs practice, and need for HPLC to measure the concentration of penetrant. Hence, this study evaluated skin penetration by fluorescence spectroscopy as an alternative method. The poorly soluble curcumin was used as a model drug.

MATERIALS AND METHODS

The curcumin was used as bulk suspension (mean size about 50 μm) and was formulated as nanocrystals by small-scale bead milling with sizes of about 250 nm. Porcine ear skin of 1,000 μm thickness was prepared using a dermatome, the skin was punched (Ø 15 mm), placed in the bottom of a 24-well plate and 10 μl of formulations were applied. The fluorescence intensity was measured in multi-point bottom read at excitation and emission wavelength of 464 nm and 550 nm, respectively, to estimate the amount of curcumin penetrating into the skin over 24h. The experiment was conducted in triplicate.

RESULTS

The fluorescence intensity at the bottom of the well-plates increased over 24 h and allowed to estimate the penetration kinetics of curcumin from the different formulations. Results show a faster and a higher penetration of curcumin through the skin from the nanocrystals when compared to bulk suspension (+143%, 159%, 140%, 124%, 116% after 30 min, 1, 8, 16, and 24 h, respectively). The results correlated to the results of a previous study and proved again that the smaller size of nanocrystals can improve the dermal penetration of curcumin [1].

CONCLUSION

Fluorescence spectroscopy was shown to be a simple, fast, and alternative tool for the assessment of the dermal penetration kinetics of curcumin. Future studies are now required to prove the versatility of the method for other chemical compounds.

REFERENCE

INTRODUCTION

The major advantage of the orodispersible films (ODFs) is short disintegration time without the need of water, which is indicating as a key factor affecting their acceptability [1]. They can be manufactured using solvent casting method, printing techniques or intensively studied in recent years electrospinning method. The electrospinning enables to obtain fibrous films with high surface area, where drug substance may be in amorphous state exhibiting improved dissolution rate [2,3].

MATERIALS AND METHODS

Aripiprazole (ARP) was used as a model drug. Poly(vinyl alcohol) (PVA) and hydroxypropyl cellulose (HPC) were used as a film forming polymer. Glacial acetic acid, ethanol and purified water were used as solvents.

The ODFs were prepared by electrospinning method using high voltage power supply SKE Research Equipment®. The voltage was between 15–25 kV, the distance between the needle and the collector was 10 cm, and the feeding rate of the spinning solution was set at 1 mL/h. The fibers were collected on the rotating metal drum collector wrapped with aluminum foil. The fibers morphology was investigated using scanning electron microscope. The properties of the films were evaluated according to their appearance, disintegration time, wettability, mechanical properties and dissolution study.

RESULTS

The smooth fibers without bead formation were obtained from the ethanolic solution of the HPC or the water solution of the PVA. The ARP incorporation to polymeric solutions was higher in the case of the PVA formulation. Applied electrospinning parameters depended on the type of the utilizing polymer. Only the PVA-based films were easy to detached from aluminum foil. They were characterized by rapid disintegration time within 1 s, good mechanical properties and high dissolution rate.

CONCLUSION

Electrospinning process enables to prepare ODFs with good mechanical properties and rapid disintegration time.

REFERENCES

HYALURONIC ACID DECORATED POLY-B-CAPROLACTONE-POLYETHYLENEIMINE NANOCARriers IMPROVE DRUG TARGETING OF NON SMALL CELL LUNG ADENOCARCINOMA POSITIVE FOR CD44 EXPRESSION

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INTRODUCTION

Multifunctional nanocarriers address multiple biological barriers to drug targeting by different functional modalities, facilitating the EPR effect with one modality and improving the efficacy of intracellular payload delivery\textsuperscript{1}. To minimize the off-target effects and improve drug targeting in NSCLC positive for CD44 expression, paclitaxel (PTX) loaded hyaluronic acid (HA) decorated poly-b-caprolactone-polyethyleneimine (PCL-b-PEI) nanocarriers were developed and characterized. HA reorganized into a nanoparticle will improve EPR effect and decrease toxicity of the carriers masking the positive charge during circulation. Tumor localization and stimulus by the acidic microenvironment will reverse the nanoparticles' charges, improving internalization and delivering the payload at the site of action\textsuperscript{2}.

MATERIALS AND METHODS

Ultrasound assisted nanoprecipitation was used for preparation of the NPs designed and optimized using D-optimal design model. Physicochemical characterization (particle size, zeta potential, in vitro drug release, drug content (DC), encapsulation efficacy (EE%), DSC studies, FTIR analysis, SEM studies). Cytotoxicity assays including MTT and LDH assays were carried out on H322 and A549 cell lines, which express low and high levels of CD44. Annexin V FITC and propidium iodide kit for flow cytometry was used for evaluation of apoptosis.

RESULTS

PTX loaded (PCL-b-PEI)HA NPs showed zeta potential of -1.2±0.4 mV (pH 7.4); 3.2±0.8 mV (pH 5.6) and particle size of 103±2.2 nm (PDI = 0.11±0.02), high DC\% (20.27\%), EE\% of 73\%, slow dissolution rate (60\% for 80h) best fitted by Korsmayer-Peppas model with n parameter pointing to Fickian diffusion. FTIR and DSC studies confirmed the conjugation of the PCL-PEI-HA and the formation of the polyelectrolyte complex and confirmed the entrapment of the PTX in the NPs core in amorphous state. A549 cells were treated with 5 or 10\(\mu\)M of paclitaxel and H322 cells treated with 500 or 1000nM. Cytotoxicity was not different in H322 cells between paclitaxel vs NPs. Whereas, the cytotoxicity was greater in A549 cells treated with loaded NPs. The LDH assay showed reduced cell membrane damage with loaded NPs in A549 cells. Flow cytometry after a two hour treatment showed slightly decreased early and late apoptosis induced in H322 cells when treated with NPs compared to paclitaxel alone as expected having in mind that the nanoparticles should be internalized and paclitaxel released in order to show it's efficacy.
CONCLUSION

Targeting CD44 positive NSCLC might be a rational approach for providing efficacious therapy with minimal side effects.

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REFERENCES


QUALITY BY DESIGN BASED FORMULATION OF INTRANASAL MELOXICAM CONTAINING HUMAN SERUM ALBUMIN NANOPARTICLES

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INTRODUCTION

Human serum albumin (HAS) as a versatile, biodegradable nano-carrier is a promising tool for nose-to-brain delivery of NSAIDs. In comparison to other colloidal drug delivery systems, they have no immunogenic effect, moreover, HSA nanoparticles with a size below 200 nm have enhanced permeation and retention (EPR) effect, which helps in passive targeting of the conjugated drug.

MATERIALS AND METHODS

Meloxicam (MEL) -HSA nanoparticles were prepared by a modified coacervation method without using organic solvents and cytotoxic crosslinking agent. The influencing factors of preparation were determined by QbD concept and the formulation was optimized using a Box-Behnken experimental design. Various properties such as particle size, zeta potential, encapsulation efficacy (EE), conjugation of MEL and HSA, physical stability, in vitro dissolution, in vitro permeability and in vivo plasma and brain distribution of MEL were characterized.

RESULTS

From a stability point of view, a solid product can be recommended for further development that has met the desired critical parameters (176±0.3 nm Z-average, 0.205±0.01 PdI, -14.1±0.7 mV zeta potential) after 6 months of storage. In vitro examination showed significantly increased drug dissolution and permeability of MEL containing nanoparticles, especially in case of applying Tween 80. The in vivo studies showed significantly higher cerebral concentration of MEL was detected with nose-to-brain delivery, in comparison with intravenous or per os administration.

CONCLUSION

These results indicate intranasal administration of optimized MEL containing HSA formulations as a potentially applicable “value-added“ product for the treatment of neuroinflammation.

ACKNOWLEDGEMENT

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DEVELOPMENT AND EVALUATION OF BIGELS CONTAINING NAPROXENE

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INTRODUCTION

Bigels are unique semi-solid formulations obtained by mixing in different proportions a hydrogel with an oleogel. The main advantage of bigels is given by the effect of the two phases of the gel that brings the ability to incorporate both hydrophilic and lipophilic substances. Bigels can be also considered as systems for controlled drug delivery. Naproxen is a non-steroidal anti-inflammatory which administration in chronic treatment increases the risk of side effects. Topical administration of naproxen as bigel is preferred in the case of long-term treatment [1-3].

MATERIALS AND METHODS

Three different formulations of bigels were prepared. Two bigels formulations with a 7:3 ratio of hydrogel:oleogel were prepared based on sodium alginate, flaxseed oil and aerosil (BGAlg1), respectively sodium alginate, coconut oil and wax for the second formulation (BGAlg2). The third formulation (BGCbp) contained a 5:5 hydrogel:oleogel ratio and was based on carbopol gel, almond oil and span 60. For all formulations, rheological properties, consistency, spreadability, pH, adhesiveness and stability under the action of intense shear forces were analyzed.

RESULTS

The obtained bigels presented a pseudoplastic behaviour and had a pH that varied between 4.6-5.5. The best spreadability was observed for formulation BGAlg1 and the highest adhesiveness capacity was observed for formulation BGCbp. Under the action of intense shear forces, the phase separation of the bigels was observed.

CONCLUSION

In this study homogeneous bigels with a pH suitable for skin application were obtained. Bigels presented also a good spreadability and a pseudoplastic behaviour.

REFERENCES

GASTROINTESTINAL PASSAGE EFFECTS ON THE MICRO-ENVIRONMENTAL pH INSIDE THE HPMC MATRIX TABLETS

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INTRODUCTION

The pH of the GIT luminal medium significantly affects the ionizable drug dissolution. The modification of the microenvironmental pH can lead to significantly better dissolution properties. Therefore the aim of our work was to prepare HPMC tablets with poorly soluble weakly acidic and basic drugs incorporating pH modifiers, to improve their dissolution and to test the influence of the mechanical effects.

MATERIALS AND METHODS

Dissolution testing: performed in two biorelevant dissolution systems, the AGS and the IMSPA, and compared USP 2 [1], media: SGF, buffer pH 6.8. Assessment of the micro-environmental pH (pHM): the cryostatic sample preparation and subsequent surface pH measurement, and 2) by incorporating pH indicator dye (methyl orange) into the tablet matrix. Model drugs: propranolol hydrochloride (pKa 9.05), dipyridamole (pKa 6.4), diclofenac sodium (pKa 3.80).

RESULTS

The HPMC tablets were sensitive to mechanical stress as seen on two model drugs (propranolol hydrochloride, dipyridamole). The biorelevant AGS and IMSPA discriminate between formulations better than the conventional USP 2. The effects of pH modifiers were more favourable in the case of basic drugs. The pH sensitive dye incorporated in tablets can clearly visualize the pH gradient in a swollen matrix system.

CONCLUSION

The pH modifying approach can substantially improve the dissolution of poorly soluble drugs [2, 3]. Our study demonstrates significant effects of GIT transit on the mechanically sensitive HPMC tablets, where the biorelevant models with pH indicators incorporated in the matrix system can truly offer a greater insight into the dissolution process.

REFERENCES
MUCAODHESIVE BUCCAL TABLETS WITH PROPRANOLOL HYDROCHLORIDE: IN VIVO PERFORMANCES IN SPONTANEOUSLY HYPERTENSIVE RATS

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INTRODUCTION
Mucoadhesive oral delivery systems improve the absorption of the drug substance by extending the residence time at the specified application site through close contact with the oral membranes [1]. Propranolol hydrochloride (PROP) is a highly soluble and highly permeable drug substance with extensive first-pass metabolism [2], thus it is a good candidate for the development of mucoadhesive dosage forms for transmucosal delivery.

MATERIALS AND METHODS
Male spontaneously hypertensive rats were divided into control group (tap water 0.5 mL; p.o.), immediate-release (IR) PROP group (10 mg Propranolol® tablet; p.o.), and extended-release (ER) PROP group (10 mg PROP mucoadhesive buccal tablets; lower pocket of the lip). Systolic pressure (SP), diastolic pressure (DP), and heart rate (HR) were registered and blood samples were collected at 0 h, 0.25 h, 0.5 h, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h, and 24 h. Maximum PROP plasma concentration, time to reach maximum PROP plasma concentration (tmax), area under the PROP plasma concentration-time curve (AUC0→t) were calculated by non-compartmental analysis.

RESULTS
Pharmacokinetic study showed the superiority of ER mucoadhesive buccal tablets over IR tablets in terms of extend of PROP absorption (AUC0→t: 70.32±19.56 vs. 31.69±6.97 μg×h/ml), as well as extended-release (tmax: 5.33±1.03 vs 0.58± 0.20 h). Hemodynamic study showed that ER mucoadhesive buccal tablets caused more pronounced decrease primarily in HR, but also in SP and DP, and longer HR reduction compared to IR tablets.

CONCLUSION
The prepared mucoadhesive buccal tablets are promising for buccal administration of PROP, allowing to bypass/reduction the extensive hepatic first-pass metabolism and thus improving therapeutic effects of PROP.

REFERENCES
APPLICABILITY OF SOFTWARE ASSISTED POROSITY EVALUATION IN LIQUISOLID PELLETS CHARACTERIZATION

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INTRODUCTION

Software assisted image analysis represents emerging approach, which may provide useful insight into sample properties [1]. However, its application in the pharmaceutical field is scarce. The aim of this work was to investigate the applicability of software assisted porosity evaluation in liquisolid pellets characterization.

MATERIALS AND METHODS

Liquisolid pellets were prepared by extrusion/spheronization. Microcrystalline cellulose was used as carrier and either crospovidone (CP) or silicon dioxide (SD) as coating agent. Ibuprofen solution in polyethylene glycol 400 was added as liquid phase, in concentration 28.6-52.2%. Scanning electron microscope (SEM) Supra 35 VP-24-13 was used for morphological examination and ImageJ software for porosity evaluation. Computer scanner Perfection V700 was used for pellet size and shape analysis. Single pellet crushing force (SPCF) was determined using the Shimadzu universal testing machine EZ-LX.

RESULTS

All pellets exhibited low aspect ratio values (1.08-1.16), satisfactory for processing [2]. The increase in liquid load led to wider pellet size distribution. The highest SPCF (0.350-0.724 N) were observed in the case of samples with 35.7% CP, which was in accordance with the dense pellet structure observed in SEM images. Increase in liquid load generally led to lower SPCF, higher porosity and wider SPAN values. Porosity results obtained by ImageJ software exhibited strong linear correlation with SPCF (R=0.9047).

CONCLUSION

Software assisted porosity evaluation was found useful as a screening tool which provides good correlation with pellets crushing force, and may be used as an indicator of pellets mechanical properties important for their further processing.

ACKNOWLEDGEMENT

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REFERENCES

IMPROVING THE DISSOLUTION RATE OF POORLY SOLUBLE MELOXICAM USING MIXING AND CO-MILLING WITH A HYDROPHILIC CARRIER

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INTRODUCTION

The aim of this work was to study the influence of mixing and co-milling with a hydrophilic carrier on the dissolution rate of the model drug (BCS class II).

MATERIALS AND METHODS

Meloxicam (MLX, solubility in water is 4.4 mg / ml at 25 °C [1]) and lactose monohydrate (LACT) were used. MLX particles are very fine with a median particle size $x_{50} = 3.7 \mu m$ and relatively narrow distribution (span = 1.94) whereas LACT has bigger columnar particles with a median size $x_{50} = 38.1 \mu m$ and a wider distribution (span = 2.54). Binary mixtures 1:1 and 1:8, respectively, were prepared either by mixing (PM) (Turbula mixer, 5 min, 34 rpm) or co-milling (CM) (Retsch planetary ball mill, 15 min, 300 rpm). The particle size and particle size distribution were estimated by laser diffraction (Mastersizer 3000) using dry cell. The flow-through cell dissolution (USP 4, phosphate buffer pH 6.8) with an open loop was used to estimate the dissolution rate of the drug (mg × dm⁻³ × s⁻¹) in the binary mixtures. The results were compared with blank samples (MLX activated by mixing or milling).

RESULTS

The dissolution rate of the drug was slightly improved by simple mixing of MLX with LACT carrier while co-milling produced higher effect. The effect was dependent on the drug-carrier ratio; 1:8 was more efficient than 1:1. In comparison with MLX:LACT 1:8 PM, the dissolution rate of MLX:LACT 1:8 CM was increased about 7 times.

CONCLUSIONS

Out of the investigated samples, the highest relative mass of dissolved drug $m_{rel} = 72.9 \%$ within 15 minutes of dissolution run and the highest maximum dissolution rate of $r_{max} = 1.1684 \text{mg} \times \text{dm}^{-3} \times \text{s}^{-1}$ were detected for MLX:LACT 1:8 CM mixture. The reason is presumably the particle size reduction associated with the MLX deagglomeration and formation of interactive mixture.

The study was supported by the projects of Charles University No. 268120/2020 and SVV 260 547, and Zentiva, k. s.

REFERENCES

PREPARATION AND PHARMACEUTICAL EVALUATION OF MULTILAYER FILMS WITH CHITOSAN/PECTIN POLYELECTROLYTE COMPLEXES FOR BUCCAL ADMINISTRATION OF CLOTRIMAZOLE

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INTRODUCTION

Polyelectrolyte complexes (PECs) are three dimensional structures composed of the oppositely charged polymers that attract a lot of attention over the last years as potential drug delivery systems [1]. Among the variety of PECs-based drug dosage forms, multilayer films composed of polycationic chitosan and polyanionic polymers of natural and synthetic origin separated by ionically interacting chains of PECs are promising delivery platforms for mucosal administration [2]. In response to the common problem of oromucosal fungal infections, the goal of the study was the development and pharmaceutical evaluation of multilayer chitosan/pectin films for buccal delivery of clotrimazole – well–known antifungal agent for prevention and therapy of mucosal and skin lesions [3].

MATERIALS AND METHODS

The films composed of high molecular weight chitosan and high methoxy amidated pectin were prepared by solvent evaporation technique. Clotrimazole was suspended in the films layers with addition of polyethylene glycol 400 and so different drug distribution was obtained. The films were pharmaceutically evaluated with regard to their microenvironment pH, drug release, swelling and physicomechanical behaviour, including tensile strength, Young’s modulus or folding endurance. Mucoadhesive properties of the multilayer systems were assessed ex vivo using porcine buccal mucosa. For the antifungal activity test, cultures of Candida albicans, C. krusei, and C. parapsilosis were used.

RESULTS

Depending on the drug distribution and pH conditions, significant disparities in clotrimazole release profile were observed. Inhibition of Candida sp. growth was noted for both drug–loaded and placebo formulations, however for all drug–loaded formulations, no significant differences in the inhibition zones were observed.

CONCLUSION

The multilayer PECs systems might be recognized as smart platforms for prolonged and pH–dependent delivery of clotrimazole. As chitosan increased antifungal activity of clotrimazole, the potential utilization of designed films in resistant cases of oral candidiasis might be worth of further exploration.

REFERENCES

IMPLEMENTATION OF RAMAN IMAGING IN THE EVALUATION OF INTERNAL MORPHOLOGY OF MICROPARTICLES PRODUCED BY SPRAY CONGEALING TECHNOLOGY

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INTRODUCTION

Raman mapping is a non-destructive technique which does not require laborious sample preparation and what is more, it can also provide extensive data about the sample. In this work, Raman imaging has been applied for investigation of internal morphology of the lipid-based microparticles, including the distribution of the two phases (hydrophilic and lipophilic) as well as the drug substance (tolbutamide) distribution within the microparticles. The samples were loaded with different amount of tolbutamide, both as solution (completely solubilized in the hydrophilic phase) or suspension (partially suspended as crystals).

MATERIALS AND METHODS

A WITec Alpha 300 Raman spectrometer connected with a confocal microscope was used in the studies. Before Raman mapping, Raman spectra for all raw materials were recorded in order to identify key marker bands for identification of tolbutamide and excipients in the investigated microparticles. The analysis based on the calculation of the integral value (area under the band) for the selected bands as well as chemometric analysis (k-means cluster analysis) were performed in order to describe a distribution of the two phases (hydrophilic and lipophilic) as well as the drug substance within the investigated microparticles produced by spray congealing technology.

RESULTS

The spatial distribution of components in drug-loaded microparticles was evaluated and visualized based on Raman mapping data supported by chemometrics. The Raman mapping allowed for a differentiation of hydrophilic and lipophilic phase in all investigated biphasic microparticles. Furthermore, their Raman maps revealed the presence of multiple hydrophilic internal cores in the lipophilic phase.

CONCLUSION

The usefulness of Raman imaging in the investigation of a spatial distribution of hydrophilic and lipophilic phase in the microparticles has been demonstrated. The distribution of tolbutamide in drug-loaded microparticles can also be evaluated. The Raman maps help better understand the influence of process and formulation parameters on the internal structure of microparticles produced by spray congealing technology.

ACKNOWLEDGMENTS:

This work was supported by the Nicolaus Copernicus University in Toruń under the Excellence Initiative - Debuts (grant IDUB 2020-1-NZ-Ronowicz).
EXPERIMENTAL DESIGN METHODOLOGY AS QUALITY BY DESIGN TOOL IN API-EXCIPIENT COMPATIBILITY SCREENING

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INTRODUCTION
The compatibility assessment of formulation ingredients is one of the crucial stages of a new drug product development process. Currently, there is still a lack of clearly defined guidelines regarding the screening of API-excipients compatibility. In research papers, the approach using binary physical mixtures as well as multicomponent physical mixtures is described. In this work, attention is directed toward so called experimental design methodology as a potentially useful Quality by Design tool for defining the qualitative composition of pharmaceutical formulations.

MATERIALS AND METHODS
The experimental work was designed using the experimental design methodology (Design of Experiments, DoE). Ketoprofen and hydrocortisone were chosen as model APIs. Several different multi-component physical mixtures were prepared according to the matrix generated by means of fractional factorial design. The mixtures were exposed to the elevated temperature and humidity in a climate chamber for 3 weeks. Four types of excipients (binders, disintegrants, fillers and lubricants) were used as input variables. The degree of API degradation (determined by RP-HPLC method) was the output variable.

RESULTS
The experimental design approach allowed for the simultaneous assessment of the influence of several excipients on API degradation, and consequently, the selection of optimal raw materials with a relatively small number of prepared mixtures. A strong influence of the type of a disintegrant on ketoprofen degradation was confirmed ($p < 0.05$). The DoE analysis also revealed that the type of a binder had a strong statistical influence on hydrocortisone degradation ($p < 0.05$). Whereas, the effect of the other type of excipients was statistically insignificant.

CONCLUSION
The DoE approach allows to better understand the influence of excipients on API degradation and select the most optimal formulation composition, while maintaining the limitations imposed on the number of experiments, and thus on the cost and timeliness of studies. The experimental design approach seems to be effective Quality by Design tool which facilitates and accelerates the preformulation stage of a new drug product development, significantly.

ACKNOWLEDGMENTS:
This work was supported by the Nicolaus Copernicus University in Toruń under the Excellence Initiative - Debuts (grant IDUB 2020-1-NZ-Ronowicz) and PDB WF 514.
EVALUATION OF FACTORS AFFECTING THE KETOPROFEN RELEASE FROM 3DP TABLETS

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INTRODUCTION

Fused deposition modeling (FDM) is one of the most promising 3D printing method in preparing personalized medicines [1]. This method allows for the preparation of dosage forms with adjustable API strength and dissolution profiles, which is particularly important i.e. during nonsteroidal anti-inflammatory drugs therapy [2]. The aim of this study was to analyze the factors affecting the ketoprofen dissolution rate from 3DP tablets.

MATERIALS AND METHODS

Ketoprofen (KET) was selected as a model drug. Poly(vinyl alcohol) was used as a water-soluble matrix-forming polymer, while Crospovidone was added as a release modifier. Co-extrusion of drug-loaded filament with Kollicoat IR-based placebo filament was applied to achieve additional drug dissolution modification.

The filaments were prepared using two-screw extruder. Tablets were fabricated using ZMorph FDM 3D printer equipped in single or dual extrusion toolhead. The effect of tablets composition, dosage and spatial structure including infill type and density on drug dissolution rate was performed in the sink conditions using a USP-II apparatus.

RESULTS

Among the analyzed factors only infill type affected the drug dissolution rate in single-extruded tablets. The fact, that other factors did not significantly affect the release of KET proves the possibility of dose customization without changing the release profile. Co-extrusion occurred more beneficial in improving drug dissolution rate than structural modifications.

CONCLUSION

High flexibility of FDM method allows for fabrication of personalized medicines with desired dosage, dissolution profile and high reproducibility.

ACKNOWLEDGMENTS

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REFERENCES

INTRODUCTION
The classic empirical approach of scientific research consisting in a large number of experimental runs can be modified by using various DOE techniques [1]. In our study, we applied a response surface design to optimize the milling process of the pharma excipients.

MATERIALS AND METHODS
Materials: HPMC K15 (Benecel K15M Pharm CR, Ashland, USA) Alginic acid (Sigma-Aldrich, Japan), Alginic acid calcium salt (Sigma-Aldrich, China), Avicel® PH-200 (FMC Biopolymer, United Kingdom), Carrageenan, κ + λ (Sigma-Aldrich, USA). Methods: the milling process was performed with planetary ball mill Retsch GmbH, PM 100, Germany; particle size measurement was performed before and after using Mastersizer 3000, the particles were analyzed by SEM and DSC.

RESULTS
In this project, the influence of the main factors of the milling process using a ball mill on five pharmaceutical excipients was investigated [2]. For optimisation of the process for two factors with five levels CCD technique was applied [3]. The prediction model and optimum values were calculated using Matlab 2021b software. The optimal was defined for each material and varied depending on its type and properties, which have also been analyzed by SEM and DSC. For three out of five excipients the best size of balls was indicated as 5 mm balls. For the rest two 2 mm and 10 mm balls gave the better outcome. As the responses three variables were evaluated (X50, X90 and span).

CONCLUSION
Using the QbD approach, we demonstrated how to optimize the milling process of pharmaceutical powders and assessed the effect of the key factors on the material. Applying CCD, the optimal conditions for obtaining the powder with the given parameters were determined.

REFERENCES
TEXTURE ANALYSIS OF BILAYER TABLETS WITH HPMC MATRIX LAYER

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INTRODUCTION

Bilayer tablets are often used in fixed-dose combination development. Separation of two drug substances could avoid chemical incompatibility and gives opportunity to create products with different release mechanisms from each layer [1]. HPMC is a non-ionic polymer that is used as a matrix forming excipient. Swelling of HPMC based matrix depends on its viscosity, and concentration of this excipient in tablet blend [2]. The aim of this research is to check how composition of immediate release layer influence on swelling of HPMC matrix.

MATERIALS AND METHODS

The test tablets consisted of HPMC based modified release (MR) layer and an immediate release (IR) layer. Two types of IR layers have been tested: lactose, and cellulose-starch-based.

Tablets were incubated in vials filled with phosphate buffer pH=4.5, 37°C temperature. After 2 hours tablets were tested using TA.XTplus Texture Analyser (Stable Micro Systems Ltd) with load cell 5kg and cylinder probe.

RESULTS

Thickness of gel layer after incubation was higher for tablets with the lactose-based IR layer. For these tablets, one-sided thickening of the gel layer was noted upon dissolution of the IR layer. Tablets with cellulose-starch-based IR layer had thinner and more uniform gel layer. They were also more resistant to mechanical stress.

CONCLUSION

In this particular case composition of the IR layer had an influence on swelling behaviour of HPMC matrix layer. Texture measurement could give valuable information about mechanical resistance, and gel thickness of matrix layer after contact with fluids.

REFERENCES

TECHNOLOGY OF ORODISPERISIBLE POLYMER FILMS AS MULTIPARTICULATE DRUG DELIVERY SYSTEMS WITH PELLETS – INFLUENCE OF DIFFERENT GRANULES LOADING ON FILM PROPERTIES

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INTRODUCTION

Orodispersible polymer films (ODFs) allow to administer active substances in a solid form easily because of the rapid disintegration in the saliva (usually <60s). They are a good alternative for tablets, especially for pediatric and geriatric patients. Although the most popular approach is to prepare ODF with dissolved active substance, a drug may be incorporated in the film as particles (crystals, nanoparticles, granules) [1,2]. The following study was conducted to investigate the possibility to formulate multiparticulate ODFs containing relatively large particles - pellets in size of 100-300 μm.

MATERIALS AND METHODS

Spherical granules (Cellets® - CL100 and CL200, with the mean size of 156 and 263 μm, respectively) (Harke, Germany), Pharmacoat 606 (HPMC) (Shin-Etsu, Japan) and glycerol 86% (GL) (Fagron, Belgium) were used. A planetary mixer (Thinky Mixer) was used to prepare polymer solution with the suspended pellets. ODFs were prepared by solvent casting technique using a film applicator (Camag, Switzerland). The influence of concentration (20-45% of dry film mass) and size of CL on the physical properties of HPMC films was evaluated using a pharmacopoeial tablet disintegration apparatus and TA.XT plus texture analyzer (Stable Micro Systems, UK). Optical microscope image stitching mode allowed to visualize the particles distribution and to determine the number of pellets per area.

RESULTS

A planetary mixer allowed to obtain homogeneous films characterized by an adequate uniformity of mass and particle distribution. ODFs containing CL100 and CL200 (gap 500 μm) disintegrated within less than 30 s, but the films with bigger granules disintegrated faster. The mechanical properties of the obtained films depended on both the CL concentration and size. The incorporation of solid particles reduced the tensile strength and flexibility of the films, but still they were easy to handle. The roughness of ODFs with pellets depended on the casting gap (500 or 800 μm) and the size of CL. The linear relationship between pellets mass concentration and density (number/area) was observed.

CONCLUSION

It was found that with HPMC matrix (produced from 15% solutions) it is possible to obtain a homogeneous multiparticulate ODFs with satisfying disintegration time and mechanical properties.

REFERENCES

DEVELOPMENT OF SELF-EMULSIFYING OILS FOR OPHTHALMIC DELIVERY OF ANTIBIOTIC INSTABLE IN WATER

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INTRODUCTION

The previous research on self-emulsifying drug delivery systems (SEDDS) have focused mainly on improving the solubility as well as the bioavailability of lipophilic drugs including topical administration to the eye [1]. The main objective of current project is focusing on developing ocular self-emulsifying suspensions as a novel approach to improve the stability of administering water-sensitive drugs, such as cefuroxime sodium (CEF), which require moisture protection during storage [2]. Safety of SEDDS for ocular administration have been already demonstrated [3].

MATERIALS AND METHODS

SEDDS carriers were obtained by dissolving surfactant (5% w/w) in Miglyol oil with subsequent dispersion of CEF (5% w/w). Cremophor EL, Span 80 and Tween 20 were surfactants tested, with or without benzalkonium chloride (0.01% w/w). The self-emulsification efficiency upon dilution with water was evaluated. The formulations were exposed to 6-months long stability testing. Physicochemical parameters: particle size, pH, Zeta potential were studied. Degradation rate of CEF was analyzed with HPLC method.

RESULTS

The SEDDS suspensions diluted with water were reported to form spontaneously fine emulsions exhibiting an immediate dissolution of cefuroxime. All formulations showed an average globule size less than 30 μm and negative zeta potential range of -40mV - -55 mV. These parameters did not change significantly during storage. Less than 2% of degradation products were determined in the formulations with Span or Tween after 6 months of storage at 40°C. The effect of benzalkonium chloride as a co-surfactant depended on the type of the main surfactant.

CONCLUSION

The developed formulations proved to be physically and chemically stable over storage and seem feasible to serve as the effective carriers for water-sensitive drugs.

REFERENCES

INTRODUCTION

Orodispensible films (ODFs) are defined as thin strips made of film-forming polymers and suitable excipients. ODFs constitute flexible drug delivery tool for pediatric and geriatric patients or those suffering from swallowing problems, enabling convenient administration of therapeutic substances due to rapid disintegration in the oral cavity (< 30sec) without drinking water, thus eliminating the risk of choking [1]. As ODFs have direct contact with the taste buds, acceptability of the taste is an important factor affecting pharmacotherapy effectiveness. Preparing microparticles (MP) using taste masking polymers, e.g. ethylcellulose (EC) is considered as efficient method for reducing the bitterness of a drug. Rupatadine fumarate (RUP) is antihistamine characterized by very bitter, unpleasant taste [2]. The purpose of the present study was to prepare ODFs containing taste masked MP with RUP in the dose of 2.5 mg required for children weighting from 10 to 25 kg.

MATERIALS AND METHODS

MP were obtained by the spray drying method with RUP and EC aqueous dispersions: Surelease® E-7-19040 or Aquacoat® ECD in drug:polymer ratio 0.5:1 [2]. ODFs were prepared by solvent casting method from solution made of hypromellose (HPMC, Pharmacoat® 606 – 12%), glycerol (50% w/w of the polymer) and water. MP-loaded films were prepared by solvent casting method utilizing automatic film applicator (Elcometer 4340), then cut into pieces (2cmx2cm) to include 2.5 mg of RUP in each ODF, then assessed for appearance, weight, thickness, disintegration time, drug content, mechanical properties and taste masking efficiency in human taste panel by 6 healthy volunteers.

RESULTS

ODFs were of milky color (due to the presence of MP), with average mass of 20 mg and thickness 60μm. The RUP content was within pharmacopoeial requirements [3]. Disintegration of ODFs occurred within 15 sec. ODFs containing MP were of weaker mechanical properties compared to placebo, but still resistant to handling. ODFs were assessed as non bitter or slightly bitter.

CONCLUSION

ODFs containing EC MP with RUP obtained by solvent casting method were characterized by acceptable taste, beneficial physicochemical properties and relevant disintegration time.

REFERENCES

THE INFLUENCE OF TEA TREE OIL ON PHARMACEUTICAL CHARACTERISTICS AND ANTIFUNGAL ACTIVITY OF PLURONIC GEL FORMULATIONS WITH KETOCONAZOLE

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INTRODUCTION

Tea tree oil (TTO) possesses a broad spectrum of antimicrobial activity against a wide range of bacteria, viruses and fungi [1]. As the increased antimicrobial activity of conventional drugs mixed with various natural substances was reported [2], the treatment of infections based on combined therapy seems to be a valuable approach. Pluronic F127 gels have gained popularity as topical drug delivery systems owning to their low toxicity, biocompatibility, high drug loading capabilities and gelling ability in physiological conditions [3]. The purpose of the study was to develop and characterize gel formulations with TTO and ketoconazole (KTZ) - a substance commonly used in the treatment of dermatological fungal infections. The effect of TTO on antifungal KTZ activity was also assessed.

MATERIALS AND METHODS

Pluronic F127 hydrogel and pluronic lecithin organogels (PLO) based on castor oil, liquid paraffin, isopropyl myristate with KTZ and TTO were developed. The prepared formulations were analyzed visually, for pH, viscosity and drug release. The ex vivo bioadhesive properties of obtained gels using hairless mice skin and the influence of TTO on antifungal activity (measured by plate diffusion method) were also assessed.

RESULTS

All gel formulations had uniform appearance, adequate consistency and bioadhesive properties. The pH value of obtained gels was in the range of 6.5-6.8, viscosity values were from 3242 mPa·s to 23399 mPa·s and TTO addition increased viscosity of all prepared formulations. The largest amounts of released KTZ were observed for Pluronic F127 hydrogel and PLO based on castor oil containing TTO. It was found that TTO improved KTZ antifungal efficiency in all gels, especially in the case of C. parapsilosis.

CONCLUSION

Based on the obtained results, it can be concluded that designed gel formulations exhibited acceptable physicochemical and application features. Formulated gels present promising potential as topical antifungal drug carriers.

REFERENCES

FUNCTIONALIZING PROTICLES TO IMPROVE DRUG RELEASE

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INTRODUCTION

Since the Covid-19 pandemic efficient drug delivery and drug release of biomolecules like DNA, mRNA or microRNAs (miRs) is even more important than ever. So-called Proticles are nanoparticulate peptide-based drug delivery systems (DDS) to carry various oligonucleotides (ODN) [1]. They basically consist of the positively charged peptide protamine and a negatively charged ODN. Due to electrostatic interaction self-assembling occurs immediately and nanoparticles are formed. Proticles based on protamine and miRs, have shown that the strong forces between the two components lead to a lack of dissociation and further to insufficient drug release. In order to face these challenges and increase the efficacy of our nanoparticles we are modifying Proticles by supplementing the classic binary system with a third component. Different functionalization strategies were evaluated and the advanced Proticles characterized.

MATERIALS AND METHODS

MiR 27a, non-targeting-control miR and fluorescence labelled miR were purchased from Dharmacon (Colorado), protamine (free base) was obtained from Sigma Aldrich (Missouri). Photon correlation spectroscopy (Zetasizer Nano Series, Malvern Instruments, Germany) was applied in order to characterize the physicochemical properties of Proticles. Drug loading capacities were determined using RP-HPLC (Agilent technologies, California) and a Gel electrophoresis system (Thermo fisher Scientific, Massachusetts). A 3T3-L1 mouse fibroblast cell line was used as cell model for in vitro characterizations.

RESULTS

Depending on the substitute and its concentration parameters like particle size, Zetapotential or pH are differing. Applied stability tests demonstrate a decreasing tendency. Nearly the whole amount of miR was bound in all tested formulations. When it comes to in vitro characterization a drastic increase in cellular uptake as well as low cellular toxicity could be found.

CONCLUSION

In order to lower the binding strength between protamine and miR, and further improve the dissociation capacity, a third component was integrated in the binary DDS. Differences in nanoparticle size, Zetapotential, pH and cellular performances could be noticed. According to the present data functionalized Proticles represent very promising candidates for successful drug delivery and release.

REFERENCES

MUCCOADHESIVE IN SITU GELLING FLUTICASONE PROPIONATE NANOSUSPENSION FOR NASAL DELIVERY BY NEBULIZATION

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INTRODUCTION

Strategies to improve nasal drug delivery include development of formulations which reduce mucociliary clearance [1] and careful selection of nasal delivery device [2]. In situ gelling nanosuspensions present combined approach to increase mucoadhesion and prolong drug retention at nasal mucosa [1]. The aim of this study is to develop an in situ gelling fluticasone propionate nanosuspension and assess its nasal deposition after spraying with jet-flow nebulizer.

MATERIALS AND METHODS

Fluticasone propionate nanosuspensions prepared by wet media milling, were mixed with pectin and sodium hyaluronate solutions at different ratios. Formulations were characterised in terms of particle size, zeta-potential, surface tension, rheological properties, in vitro biocompatibility using Calu-3 cells, mucoadhesiveness with porcine mucosa and nasal deposition pattern using a jet-flow nebulizer and a 3D printed nasal cast.

RESULTS

In situ gelling fluticasone propionate nanosuspensions were characterised by particle diameter between 140.3 to 166.8 nm, zeta-potential between –89.5 and –83.2 mV and surface tension of about 37 mN m⁻¹ at 25 °C. Rheological studies confirmed the gelation of formulations when mixed with simulated nasal fluid. The formed gel showed appropriate strength and stability profile. All formulations were biocompatible (cell viability > 90%) and mucoadhesive. Spraying the formulations with jet-flow nebulizer resulted in targeted deposition within the 3D printed nasal cast.

CONCLUSION

Biocompatible in situ gelling fluticasone propionate nanosuspensions have been successfully prepared. Their rheological properties imply instant gelling in contact with nasal fluid, which, combined with mucoadhesive properties, indicate the potential for extended residence time at nasal mucosa. Nasal deposition profiles proved the suitability of jet-flow nebulizer for nasal delivery of in situ gelling nanosuspensions.

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REFERENCES

OPTIMIZATION OF ELECTROSPUN NANOFIBER PRODUCTION USING CIPROFLOXACIN AS A MODEL DRUG

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INTRODUCTION

Nanofibers, innovative drug delivery systems are mainly produced by electrospinning (ES) which is a relatively simple and cost-effective technique. In ES, electric field is applied to produce nanoscaled fibers containing the drug in a polymer matrix. The easiest way to form nanofibers from electrospinning solution is by single-needle ES, where fibers are formed through a nozzle. The productivity of single-needle ES is low. In contrast, nozzle-free equipment can increase the productivity of ES and could be used for massively producing nanofibers. Our aim was to produce rapid-release nanofibers by single-needle ES and then to increase productivity by transporting the method into a nozzle-free ES.

MATERIALS AND METHODS

In our work, we prepared PVP-based nanofibers loaded with ciprofloxacin (CIP). During single-needle ES, nanofibers were prepared with different flow rates and with different wt% of CIP [1]. For nozzle-free ES self-developed equipment was used [2].

RESULTS

The fiber size and morphology were optimized. Structural characterization confirmed the amorphous state of CIP. The nanofibers demonstrated a significant increase in in vitro solubility both in water and pH 7.4 buffer solution. Single medium and two-stage biorelevant dissolution studies were performed, and the release mechanism was described by mathematical models. The drug distribution within the nanofiber mats investigated by Raman mapping was found to be more homogenous from the nozzle-free method. None of the tested nanofibers were cytotoxic.

CONCLUSION

Fast-release CIP-loaded nanofibers by single-needle ES were prepared, the drug content was increased up to 10 wt%. Also, the productivity of ES was increased to facilitate industrial production.

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REFERENCES

EFFECTS OF MONOCLONAL ANTIBODY CONCENTRATION AND TYPE OF BULKING AGENT ON CRITICAL QUALITY ATTRIBUTES OF LYOPHILISATES

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INTRODUCTION

Biopharmaceuticals with monoclonal antibodies (mAb) represent one of the fastest growing areas in the pharmaceutical industry. In recent years there has been an increasing trend towards subcutaneous (SC) delivery of mAbs versus intravenous administration. The development of highly concentrated formulations is a major requirement for SC injection. Lyophilisation represents the method of choice for drying such formulations, but it is time and energy consuming process, thus it should be optimised [1, 2].

MATERIALS AND METHODS

Formulations with different mAb concentrations with sucrose and in some cases with mannitol/phenylalanine/isoleucine were prepared and lyophilised. The solutions were characterised using differential scanning calorimetry and viscosity measurements (viscometer-rheometer-on-a-chip). The stability was determined by size-exclusion chromatography and dynamic light scattering. Reconstitution time of lyophilisates was evaluated.

RESULTS

The results revealed that the viscosity of the solution increases exponentially by increasing mAb concentration, while increased concentrations of the mAb did not significantly increased the glass transition temperature of the maximally freeze-concentrated solution. Although the reconstitution times of lyophilisates were greatly increased by the increased mAb concentrations, the stability of all formulations was preserved. According to addition of amino acids it was found that the ratio between phenylalanine (or isoleucine) and sucrose of 1:4 is high enough to obtain lyophilisates with acceptable appearance and stability. Moreover it was demonstrated that isoleucine shows a good potential for mannitol replacement in low-concentrated protein formulations.

CONCLUSION

The present study demonstrates that selection of the appropriate excipients is of great importance for lyophilisates in order to achieve acceptable critical quality attributes of the product and to provide stability of mAbs. In highly-concentrated protein formulations the selection of excipients still represent a challenge.

REFERENCES

IN VITRO CYTOTOXICITY EVALUATION OF NANOLIPOSOMES INTENDED FOR BRAIN DRUG DELIVERY

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INTRODUCTION

Despite the huge potential for clinical application in the recent years, many studies have confirmed the ability of different types of nanoparticles (NPs) to accumulate in cells and induce organ-specific toxicity which is dependent on their composition and biophysical properties. These studies, combined with the ever-increasing human exposure, impose an urgent need for design of safe NPs and development of strict guidelines for their toxicity testing [1].

MATERIALS AND METHODS

Two different formulations of nanoliposomes (NLs) (soybean lecithin, hydrogenated soy phosphatidylcholine, cholesterol and LIPOID PE 18:0/18:0-PEG 2000 (NL1) or poloxamer 407 (NL2) in mass ratio 17.3:1:1:2, accordingly) were prepared by the modified lipid film hydration technique and analyzed in terms of particle size, particle size distribution and zeta potential (Zetasizer Nano-Series, Malvern Instr. Ltd., UK). The biocompatibility of NLs was investigated through determination of the cytotoxic effect on human cerebral microvascular endothelial cell line (hCMEC/D3) (CELLutions, Biosistems/Cedarlane®, Canada) by performance of MTS and LDH assays (Promega, USA) according to standard protocols.

RESULTS

NLs samples had mean particle diameter (D50) ~120 nm, following narrow unimodal distribution with negative values for zeta potential of -26.5 and -31.2 mV for NL1 and NL2, respectively. The results from the MTS and LDH assays implied that there was no reduction of the cell viability and showed low percent of cytotoxicity, accordingly, after 4 h incubation of the prepared samples in three concentrations (0.1, 10 and 100 μg/ml) with hCMEC/D3 cell line.

CONCLUSION

Obtained results from the cell viability and cytotoxicity studies confirmed the biocompatibility of NLs in the examined concentrations, which makes them suitable further to be used in the investigations of their uptake by hCMEC/D3.

REFERENCES

APPLICATION OF IONIC POLYMERS IN THE FORMULATION OF FREEZE-DRIED OROMUCOSAL DISCS

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INTRODUCTION

Lyophilization is a drying method where moisture is removed from the product by a process of sublimation and desorption [1]. Most of the freeze-dried pharmaceutical products are intended for parenteral administration, however lyophilization is used more and more often also to produce solid forms (discs/tablets) applicable locally in the oral cavity [2].

Aim of the study was to determine the structural, mechanical and mucoadhesive properties of oromucosal discs formulated with two ionic polymers: sodium carmellose and chitosan, by the freeze-drying method.

MATERIALS AND METHODS

To obtain mucoadhesive discs the 2% aqueous solutions of sodium carmellose (CMC, of low (L), medium (M) and high (H) viscosity) and chitosan (CS) were freeze-dried in PVC blisters (15 mm diameter and 6 mm height). Formulations “placebo” and with lidocaine HCl (LID) were prepared. Mechanical (resistance to compression) and mucoadhesive (attachment to the gelatin layer) properties of discs were tested using TA.XT Plus Texture Analyser. Microscopic methods (stereoscopic and SEM) were used for evaluation of the internal structure of the matrices.

RESULTS

Freeze-drying of CMC and CS solutions lead to the formation of porous discs. Their structure and mechanical properties depended on the composition of the solution subjected to sublimation. The hardest matrices were obtained from CMCH and CS solution (13.8 mJ and 12.6 mJ, respectively), while the lowest work of compression was measured for CMCL and CMCM discs (9.5 mJ and 9.6 mJ, respectively). Incorporation of the active substance into the matrices resulted in a 2-3-fold increase in the force required to discs’ deformation (this effect was not observed for CS formulations). The in vitro tests indicated that discs made of CMCM, CMCH and CS adhered to the mucosa stronger (work of detachment in the range of 0.3-0.4 mJ) than matrices made of CMCL (up to 0.17 mJ).

CONCLUSION

The ionic polymers: CMC and CS can be used for the formulation of stable, mucoadhesive freeze-dried discs intended for oromucosal application. Into these matrices LID can be incorporated even in the 1:1 mass ratio.

REFERENCES

INTRODUCTION

In Fused deposition modelling (FDM), the filament of the thermoplastic materials is melted or softened, then extruded from the printer’s head, and layer by layer deposited to form the 3D object (1). The aim of this work was to evaluate the behavior of paracetamol-loaded filaments using FDM 3D process, variating two polymers with different molecular weights.

MATERIALS AND METHODS

Four types of formulations were prepared: first - Polyox® WSR N80, arabic gum; second - Polyox® WSR N10, arabic gum; third - Polyox® WSR N80, Gelucire® 44/14; fourth - Polyox® WSR N10, Gelucire® 44/14. Paracetamol was added gradually in every type of formulation (20%, 40%, 50%, 60%, 70% w/w). The amount of Gelucire® 44/14 and arabic gum was constant (5% w/w). Manually prepared mixtures (15 g) were extruded using a Noztec pro extruder (Noztec, UK), and obtained filaments were evaluated on drug content and breaking distance (three-point bend test). Tablets (10x10x3.02 mm) were printed using the Ultimaker3 FDM printer (Ultimaker, Netherlands) with modified settings of the software and then evaluated on drug release (n=3, USP II, 500 ml of purified water, 50 rpm).

RESULTS

Extrudability was obtained with formulations contained up to 60% w/w paracetamol and it was observed that a higher amount of paracetamol and presence of Gelucire® 44/14 required higher extrusion temperature. The highest extrusion temperature (150 ºC) was required for formulation with Gelucire® 44/14, Polyox® WSR N10 and 60% w/w of paracetamol. Polyox WSR N10 was not printable in combination with arabic gum, thus printing of the second type of formulation was not possible. It was concluded that Polyox® WSR N80 is more suitable polymer for printing tablets from filaments with higher paracetamol content than Polyox® WSR N10. It was assumed that in most filaments value of breaking distance, as mechanical characteristic in three-point bend test, needs to be higher than 0.7 mm for successful printing. Drug content in printable filaments was from 80.00% to 111.87% of the theoretical content. From 3D paracetamol tablets, more than 90% of the drug was released within 4 h to 6 h by a combination of diffusion and erosion process.

CONCLUSION

FDM technology is suitable for printing paracetamol tablets with drug content up to 60% w/w and with released 90% of the drug after 4 h to 6 h. Mechanical characteristics have influence on printability, with the observation that Polyox® WSR N80 in combination with Gelucire® 44/14 is more suitable for printing.

REFERENCES

OIL MARBLES AS AN ENCAPSULATION TECHNIQUE FOR PREPARING SOLID LIPID FORMULATIONS: APPLICATION AND PRODUCTION

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INTRODUCTION
Lipid formulations such as self-emulsifying drug delivery system (SMEDDS) are potentially used for active pharmaceutical ingredients (API) with poor water solubility. We have developed an encapsulation technique based on liquid marbles-liquid droplets covered in solid particles. This work summarizes preparation of oil marbles containing abiraterone acetate, a prodrug with low bioavailability and with a considerable food effect.

MATERIALS AND METHODS
Natural and synthetic oils and surfactants were mixed together and melted at 55°C, then a linear pump was used to produce droplets via 25G needle onto HPMC-AS particles. After coating and solidification the oil marbles were sieved apart. API release was performed in various media and Wistar rats were used for the in vivo tests.

RESULTS
Oil marbles of various diameters were prepared, then basic solid-state characterization was carried out and a low amount of crystalline abiraterone acetate was detected. All dissolutions were compared to commercial product Zytiga. API release at fasted and fed conditions showed similar dissolution profiles so the food effect was eliminated. A layer of HPMC-AS polymer on the marble’s surface prevented dissolution at low pH, therefore AA recrystallization in neutral pH was suppressed. Then formulation was further subjected to in vivo study, where AUC of oil marbles increased 2,4 times compared to the commercial product and the food effect was eliminated.[1] Since no currently existing device is able to prepare oil marbles, we have been developing our own device for the mass production.

CONCLUSION
In vivo study confirmed the benefits of Oil marbles, which are capable of increasing bioavailability and eliminating the food effect. Processability is also improved, since oil marbles behave like individual particles and are more suitable for handling. Construction of a device for mass production is currently in progress.

REFERENCES
INTRODUCTION

Atopic dermatitis (AD) is a widespread chronic inflammatory skin disease, which places a significant burden to patients and to health-care costs worldwide (1). Considering adverse effects related to topical corticosteroids as the mainstay therapy for mild to moderate AD and limited skin barrier-strengthening effect of conventional formulations, there is an increasing interest for novel dermal delivery systems which can remarkably improve therapeutic outcome (2). In that regards, lyotropic liquid crystals (LLCs) with lamellar structure can be used as advanced dermal delivery systems (3) capable of restoring skin barrier function when composed of constituents with beneficial properties for AD skin.

MATERIALS AND METHODS

LLCs were developed from flaxseed oil as a lipid phase, Tween 80 and lecithin as a surfactant phase, and bidistilled water as an aqueous phase. Betamethasone dipropionate (BD) was used as a model drug. A pseudoternary phase diagram was constructed using a water titration technique. Selected unloaded and BD-loaded samples were characterized with polarized light microscopy (PLM) and rheological techniques. In addition, preliminary tests of individual components regarding their biocompatibility were performed on a keratinocyte cell line.

RESULTS

Mixtures of flaxseed oil with high content of essential fatty acids known for their anti-inflammatory activity, biocompatible surfactants, and bidistilled water formed a large region of lamellar mesophases identified in the constructed phase diagram and confirmed by PLM and rheological characterisation. Obtained LLCs were found suitable for delivery of BD, although certain structural alterations were observed upon its incorporation. In vitro cytotoxicity evaluation of individual compounds showed a great potential of the prepared LLCs as a skin compliant and barrier-strengthening delivery system.

CONCLUSION

Flaxseed oil was found suitable for formulating LLCs with BD for supportive care of atopic skin. Obtained data are valuable for further development of the delivery system, which would enable improved therapeutic outcome and patients’ compliance.

REFERENCES

IN VITRO PERMEATION STUDY OF DIAZEPAM AND INCLUSION COMPLEX FROM ORODISPERSIBLE TABLETS

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INTRODUCTION

Diazepam (D) is very useful in suppressing febrile and epileptic convulsions [1]. The introduction of orodispersible tablets (ODTs) can further expand its use to prevent febrile seizures or serial seizures at home. ODTs have improved patient compliance, convenience, bioavailability and rapid onset of action. The aim of the present study was to investigate the in vitro permeability of D and inclusion complex D with 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD) from formulated ODTs by direct compression method (ODT1 - D alone, ODT2 - D:2-HP-β-CD 1:1), primarily at pH of saliva, using the appropriate in house developed in vitro passive absorption model [2].

MATERIALS AND METHODS

The ODT1 and ODT2 were transferred to the acceptor compartments (HPLC vials) adjusted on each paddle of dissolution tester ERWEKA DT 800 (ERWEKA GmbH, Germany) and positioned vertically with polytetrafluoroethylene (PTFE) (Sartorious, Germany) artificial membrane downside oriented into dissolution vessel, as donor compartment. Three PTFE filters of vials were impregnated with mixture of phosphatidylcholine and cholesterol. The fourth was blank, with uncoated filters [2, 3]. Quantification of D was performed by UV/VIS spectrophotometric method (Perkin Elmer LAMBDA 18, Italy) at 240 nm (pH 1.2) and 230 nm (pH 4.5 and 6.8) so the apparent permeability coefficient (Papp) was calculated.

RESULTS

The Papp of ODT2 at pH 1.2 (after 1 h/2 h 3.17/3.07 × 10⁻⁴ cm/s) and 4.5 (after 1 h/2 h 2.97/2.55 × 10⁻⁴ cm/s) were lower that Papp of ODT1. At pH 6.8, an increase in the Papp of ODT2 (after 1 h/2 h 2.28/1.95 × 10⁻⁴ cm/s) relative to ODT1 was studied (after 1 h/2 h 1.73/1.28 × 10⁻⁴ cm/s).

CONCLUSION

After administration of ODTs, absorption of diazepam from ODT2 via the oral mucosa could be expected, while better absorption of D from ODT1 would be achieved in the stomach.

REFERENCES

INFLUENCE OF DRUG LAYER EXCIPIENTS ON PANTOPRAZOLE PELLETS STABILITY

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INTRODUCTION

There are numerous reasons for applying enteric coating on dosage forms, including the protection of acid-sensitive drugs, such as proton pump inhibitors (PPIs) [1]. Several factors that may affect the drug release from enteric coated dosage form can lead to inter- and intra-individual variability. One of the ways to prevent intra-individual variability is to design multiparticulate dosage forms [2].

Pantoprazole is a PPI that can be used for the treatment of acid-related gastroduodenal disorders [3]. The aim of this paper was to investigate the influence of different excipients on the formulation of stable pantoprazole pellets, as pellets can be packed more uniformly into capsule shells, ensuring more accurate dosing and patient compliance.

MATERIALS AND METHODS

Pellets were prepared by solution/suspension layering. Formulation 1 (F1) contained micronized talc as anti-tacking agent in concentration and 15.7%, in the active layer. In addition to 27.3% talc, Formulation 2 (F2) contained 16.7% povidone K25. The second, inert seal-coat and third enteric coat containing Eudragit® L30 D-55 were applied afterwards.

The influence of excipients on the stability of prepared formulations was accessed throughout the conduction of stress tests for 1 month at 55°C/75% RH.

RESULTS

After 1 month, F1 showed a significantly different colour (yellow orange compared to off-white at the beginning), and a 7.2% decrease in pantoprazole assay. Changes in colour (pale yellow compared to off-white) and 4.19% decrease in assay observed for F2 were not significant. F1 and F2 showed a similar decrease in acid resistance after 1 month (0.8% compared to 5% and 0.9% compared to 6%, respectively) and dissolution (89.5% compared to 92.5% and 85.5% compared to 92.5%, respectively), which were within acceptable limits.

CONCLUSION

The stress test showed that a higher concentration of talc in the drug layer and the presence of povidone K25 can improve the stability of pantoprazole pellets.

REFERENCES

DEVELOPMENT OF POWDER NASAL FORMS FOR DONEPEZIL HYDROCHLORIDE: FORMULATION PARAMETERS IMPACT

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INTRODUCTION

Donepezil hydrochloride (DH) is widely used for the symptomatic treatment of Alzheimer’s disease (AD), currently available only in form for oral administration. Oral administration of DH presents low bioavailability in the brain, first-pass metabolism and unwanted gastrointestinal side effects [1]. Nasal delivery of DH proposes an alternative route of administration directly to central nervous system. Nasal powders have shown encouraging results in nose-to-brain drug delivery [2]. The purpose of this study is to set the basis in the development of powder delivery platform suitable for DH nasal delivery.

MATERIALS AND METHODS

DH nasal powders were prepared by spray drying using Büchi Mini Spray Dryer B-290, equipped with ultrasonic nozzle. Spray dried solutions contained DH, low molecular weight chitosan and/or mannitol or lactose monohydrate. Microspheres were characterized in terms of entrapment efficiency, particle size and zeta potential, flow properties and spray cone angle. Nasal deposition studies were performed using a representative 3D printed nasal cast connected to respiratory pump simulating breathing conditions.

RESULTS

DH nasal powders have been successfully prepared. Under formulation, process and administration parameters employed, appropriate window of particle size (about 10 μm), flow properties (Hausner ratio between 1.16 and 1.25) and spray cone angle (17.5-19.8º) was reached resulting in targeted deposition pattern within the nasal cavity.

CONCLUSION

Preliminary studies revealed the formulation parameters to be included in experimental design aiming to enlighten a relation of DH nasal powder properties to deposition pattern. Such an approach potentiates the development of DH nasal powder delivery platform with built-in qualities, maximizing cost and time saving.

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REFERENCES

MACROPOROUS SIO2 AND NANOCRYSTALLINE CELLULOSE AS MATERIALS FOR DRY EMULSION RECONSTITUTION AND FLOWABILITY ENHANCEMENT

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INTRODUCTION

A new combination of two matrix materials, i.e. nanocrystalline cellulose (NCC) and macroporous silica (MS), was employed to produce dry emulsion powders with enhanced drug dissolution and flow properties.

MATERIALS AND METHODS

A previously developed dry emulsion formulation was chosen as the starting point¹. NCC and MS were characterised, included in the formulation (in combination and alone) and studied with respect to the process yield, drug encapsulation, reconstitution, drug release and flow properties via a response surface DoE study. NCC was added to stabilise liquid emulsion during drying and to ease oil phase release from MS. MS was added to improve flow properties, mainly due to its particle size. Mercury intrusion porosimetry was employed to assess the formulation component effects on MS porosity. Energy-dispersive X-ray spectroscopy was used to determine the presence and spatial distribution of formulation components. Flow properties, as one of our main critical quality attributes, were assessed by Hausner ratio and avalanche testing. Finally, drug release studies were performed.

RESULTS

Soluble matrix formers (mannitol, HPMC) were more efficient in encapsulating oil droplets compared to MS, and NCC didn’t have a significant effect on encapsulation efficiency. MS did strongly improve flow properties, as a consequence of particle size and density increase, however, MS did significantly deteriorate simvastatin release by entrapping it in the pores, not allowing its complete release. Addition of NCC impaired flow properties, due to the rod shape particles, however, it did improve simvastatin release. The latter is a consequence of NCC filling a portion of the inner part of the pores, enabling easier desorption of oil phase.

CONCLUSION

MS and NCC are biocompatible materials with great potential for encapsulation of dry emulsion systems. Each component is advantageous regarding product characteristics, such as flow properties and drug release. However, some disadvantages are still evident and the sole combination of MS and NCC doesn’t solve them. Further processing approaches or combinations with other materials should be explored and tested in order to overcome them.

REFERENCES

INFLUENCE OF HUMIDITY ON THE DISSOLUTION RATE OF LAMOTRIGINE IMMEDIATE-RELEASE TABLET FORMULATIONS

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INTRODUCTION

The influence of low and high humidity and different concentrations of magnesium stearate (MgST) as a lubricant and sodium starch glycolate (SSG) as a superdisintegrant on the dissolution profile of directly compressed lamotrigine tablets was investigated.

MATERIALS AND METHODS

Direct compressed tablets of 25mg lamotrigine (LMT) were prepared by mixing LMT with different concentration of MgST (0.25% and 5%) and SSG (0.5% and 4%) with microcrystalline cellulose (MCC) (Vivapur®101) or spray-dried lactose (LAC) (SuperTab 21AN) as filler. Eight tablet formulations (T1-T8) were stored for 7 days at room temperature (25°C ± 2°C) with increased (75% ± 5%) and decreased (30% ± 5%) humidity.

Dissolution characteristics in tablet formulations were evaluated at two points in the range of physiological pH (pH 1.2, pH 6.8).

RESULTS

Storage conditions at increased and decreased humidity did not significantly affect the release of LMT from formulations with high level of SSG, whereas at formulations with high level of MgST the release of LMT was reduced. Formulations with LAC showed stable release after exposure to storage conditions of increased and decreased humidity, except for the formulation with high level SSG and low level MgST.

Formulations with MCC and high level of SSG have the most stable release profile after exposure to storage conditions at different humidity levels, while formulations with low level SSG have a reduction of LMT released in both cases.

CONCLUSION

It was observed that in LMT tablets the effect of storage in high and low humidity storage conditions showed a difference in the dissolution profile and depended on the concentration of MgSt, SSG and the type of filler.

ACKNOWLEDGMENT

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INTRODUCTION

Pertussis or whooping cough caused by Bordetella pertussis remains a serious health concern despite high global vaccination coverage [1]. Commercially available pertussis vaccines are administered parenterally. Although this application elicits a systemic immune response, it often does not induce antigen-specific mucosal immunity [2]. The sublingual or buccal routes can induce mucosal and systemic immunity against pathogens such as B. pertussis that enter the body through the mucosal membranes [3]. The aim of the work was a development of a matrix for oral freeze-dried vaccine formulation with suitable mechanical and application properties.

MATERIALS AND METHODS

Dextran 40, ı-carrageenan and povidone (P) were obtained from Sigma-Aldrich. Macrogol 300 (MG), glycerine 85% (G) and sodium saccharine were obtained from Dr. Kulich Pharma. All substances were dissolved in water for injection at 40 °C to achieve appropriate concentrations (% w/w). Dipotassium phosphate (KHP) or citratephosphate buffer (CPB) was used to achieve approximately neutral pH and to modify a taste. The prepared liquid matrices were mixed with the cellular B. pertussis vaccine strain suspension (CBPV) in the ratio 1:1.

The pH (pH meter HI 221, Hanna Instruments, US) and taste of the liquid matrices were evaluated. For this purpose, the active ingredient was replaced with isotonic sodium chloride. Viscosity of liquid matrices was measured with rotational rheometer Kinexus Pro+ (Malvern Panalytical Ltd, UK) at 37 °C and shear rate 0.1 s⁻¹. The prepared mixtures (0.5 ml) were filled into Al blister and freeze-dried (Triad, Labconco, US). One complete dose was in two tablets. Lyophilization was completed in 24 h. Tablets with CBPV were evaluated for mechanical resistance (visually), water content (Ph. Eur., 2.5.12.) and disintegration time (modified Ph. Eur. method 2.9.2).

RESULTS

Crystalline carrageenan and amorphous dextran were used as structure forming excipients. Moreover, dextran as a cryoprotectant helps to protect the active substance during the freezing process. Amorphous plasticizers P, MG and GL were used to reduce the brittleness of the cake. These substances also affect viscosity and can modify the adhesion to the oral mucosa. Saccharin was used as a sweetener. Out of ten prepared samples, only matrices with KHP and with 0.5% MG, 1.0% P, 2.0% P or 1.0 % GL had an acceptable taste and pH (6.05–7.4), which is desirable for oral administration. Therefore, only these samples were used for further testing. All tablets disintegrated within prescribed time (180 s). The water content of the tablets ranged from 5.75 to 8.97%. The viscosity values were 310, 560, 1490 and 450 mPa·s for matrices with 0.5% MG, 1.0% P, 2.0% P or 1.0 % GL, respectively. High viscosity is a precondition for ensuring the sufficient contact with the oral mucosa, however, the matrix with 2.0% P was too viscous, which caused difficulties in sample preparation. All tablets were easily removed from the blister and had a visible porous structure and acceptable mechanical resistance, except for the matrix with GL, which was too brittle.
CONCLUSION
B. pertussis infects the respiratory tract. Therefore, it is reasonable to focus research on finding a dosage form that may lead to the induction of mucosal immunity. Proposed matrices composed of dextran and carrageenan with macrogol or povidone as plasticizers provided matrices with a mechanically resistant porous structure, high viscosity and a suitable disintegration time.

ACKNOWLEDGEMENTS
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REFERENCES
ONE-STEP NANOPRECIPITATION METHOD FOR SYNTHESIS OF ROSUVASTATIN AND EZETIMIBE LOADED LIPID POLYMER HYBRID NANOPARTICLES

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INTRODUCTION

The therapeutic efficacy of lipid-lowering agents as a fixed dose combination has proven more effective than monotherapy with either of the drugs [1]. Taking in consideration the uprising trends on the new generation of lipid polymer hybrid nanoparticles (LPHNPs) and rosuvastatin and ezetimibe pharmacokinetic and pharmacodynamic profile, which could be improved by their incorporation in such nanocarriers, was a challenge to develop a robust drug delivery platform with high encapsulation efficiency [2]. The purpose of the present study was to produce dual-drug loaded LPHNPs by the use of a simple nanoprecipitation method.

MATERIALS AND METHODS

Ester and COOH terminated poly (DL-lactide/glycolide copolymer with MW:45-80000, (50:50)), hydrogenated soybean phosphatidylcholine, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[metoxy(polyethylene glycol)-2000] (DSPE-PEG2000) were used for the nanoparticle preparation. Acetonitrile solution of active ingredients polymer was drop-wise added into the lipid aqueous dispersion while mixing, allowing self-assembly of nanoparticles to occur. Different concentrations of each ingredient, and different lipid or active substance to polymer ratios were tested for their influence on nanoparticle size, zeta potential (Malvern Zetasizer Nano ZS) and encapsulation efficiency (HPLC analysis).

RESULTS

Self-assembly of nanoparticles in reproducible manner was achieved, with encapsulation efficiency up to 75.13% for rosuvastatin calcium and 90.97% for ezetimibe. Nanoparticle size was in the range from 98 to 158 nm, PDI from 0.13 to 0.29, and zeta potential from 0 to -24 mV. Slightly negative zeta potential qualifies the nanoparticles as adequate for hepatocyte targeting [3].

CONCLUSION

Results obtained indicate good potential for further application in a controlled delivery therapy to the hepatocytes with adequate ligand coupling and with lower risk for phagocyte clearance.

REFERENCES

STABILITY OF LACTOFERRIN IN AQUEOUS SAMPLES

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INTRODUCTION

Lactoferrin (Lf) is an 80 kDa multifunctional iron-binding globular glycoprotein that is widely represented in various secretory fluids. The interest in products containing Lf is increasing due to its potential for the treatment of various diseases [1]. However, Lf is prone to degradation which critically affects the quality of products. Therefore, our work aimed to evaluate its stability in various samples at various storage conditions.

MATERIALS AND METHODS

The validated reversed-phase HPLC method utilized a BioZen™ Intact XB C8 column (150×4.6 mm, 3.6 μm; Phenomenex) at 30 °C and a gradient elution (0.1% TFA in water and acetonitrile) at a flow rate of 1.0 mL/min. Analysis was performed on Agilent 1100/1200 series HPLC systems, equipped with a diode array detector. Detection was carried out at 280 nm. Commercially available capsules containing Lf as well as solid and liquid Lf samples isolated from whey were tested.

RESULTS

The forced degradation study showed that Lf was most prone to degradation under alkaline and thermal conditions and at least affected by exposure to light. Up to three degradation products were detected in various samples. Lf degradation followed the zero-order kinetic model and the Arrhenius equation was linear between 60 and 80 °C. Changes in the degradation mechanism of Lf occurred between 50 and 60 °C. The rate constants were more than two orders of magnitude lower at real storage conditions compared to temperatures above 50 °C. The samples were predictably less stable at room temperature than in the refrigerator or in the freezer. Significant differences in Lf stability among various samples were observed. The concentration of Lf did not affect its stability.

CONCLUSION

Temperature is one of the main factors affecting the Lf stability. Changes in degradation mechanisms and rate constants at different temperatures were observed. Lf stability in various samples was also affected by the presence of other (protein) impurities or different salt concentrations but not by Lf concentration.

REFERENCES


ACKNOWLEDGMENTS

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DESIGN AND EVALUATION OF NEW NSAID PATCHES

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INTRODUCTION

Transdermal systems (TTS) represent an attractive therapeutic approach for patients manifesting intolerance towards oral administration, but also in situations requiring enhanced patient compliance and reduced adverse effects. By its mechanism of action, indomethacin (Ind), a NSAID, has clinical indications in joint diseases and exhibits gastric side effects [1-2]. The aim of the present work is the development of Ind containing TTS and to analyse the liberated amount of Ind based on the area under the curve (AUC).

MATERIALS AND METHODS

By solvent casting method three different polymer based formulations were prepared containing 0.5% Ind (Sigma Aldrich, Italy). Formulation F1 contains 3% HPMCE5 (Dow Chemical Co., USA), F2 1% HPMC15k (Shin-Etsu Chemical Co., Japan), and formulation F3 1.5% HPMC15k. In vitro dissolution studies were carried out using a Franz diffusion cell at a pH of 5.5 and 7.4. For each dissolution curve, AUC values have been calculated.

RESULTS

Analysing the dissolution curves based on the AUC values allows a comparative analysis of the liberated amount of Ind from the TTS. AUC varies depending on the pH of the dissolution medium, and also on the type of matrix forming polymer. At pH 5.5 the AUC (μg·min) values were: F1=366; F2=172; F3=99. At pH 7.4 the AUC (μg·min) values were: F1=1264; F2=1719; F3=1252.

CONCLUSION

Higher AUC values were obtained at pH 7.4, indicating a higher liberated amount at pH 7.4 as compared to those at pH 5.5. At pH 5.5 AUC values decrease with the increase of polymer viscosity (F1<F2<F3). At pH 7.4 AUC values decrease in the order F2<F3<F1.

REFERENCES


ACKNOWLEDGEMENT

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RHEOLOGICAL AND TEXTURAL ANALYSIS AS TOOLS FOR INVESTIGATION OF DRUG-POLYMER AND POLYMER-POLYMER INTERACTIONS ON THE EXAMPLE OF LOW-ACYL GELLAN GUM AND MESALAZINE

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INTRODUCTION

One of the parts and key steps in the design of new drug dosage forms is the identification and thorough explanation of mutual interactions between the ingredients of the preparation, both with the regard to the active compound and the excipients. The present work aimed to perform the detailed rheological and textural analysis of gellan gum-based hydrogels containing mesalazine with the regard to their potential use in the preparation of colonic beads or in situ gelling systems for the drug [1,2]. Additionally, hydrogel-forming components were used, namely hydroxyethyl cellulose (HEC) and κ-carrageenan (CAR). Moreover, the mechanical properties were investigated in the presence of two gelling agents, Ca²⁺ and Mg²⁺ cations.

MATERIALS AND METHODS

The hydrogels contained low-acyl gellan gum or its mixtures with hydroxyethyl cellulose or κ-carrageenan. CaCl₂ and MgCl₂ were used as gelling agents. Mesalamine was used as a model drug. The rheological analysis included oscillatory stress and frequency sweeping. The texture profile analysis was performed to calculate texture parameters [3].

RESULTS

Placebo gels without the addition of gelling agents had the weakest structure. The drug had the strongest ability to increase the stiffness of the polymer network. The weakest structure revealed the placebo samples without the addition of gelling agents. Texture analysis revealed no significant influence of the drug on the strength of the gels, while rheological measurements indicated clear differences.

CONCLUSION

It can be concluded that in the case of some parameters methods correlate, i.e. the effect related to gelling ions. However, the rheological analysis seems to be more precise and sensitive to some changes in the mechanical properties of the gels.

REFERENCES

INTRODUCTION

Antioxidants are major ingredients in many cosmeceutical products [1]. They increase skin resistance toward oxidative stress and protect the skin against inflammation and photoaging [2]. The current approaches to evaluate the antioxidants effect after topical application are limited, not feasible, and often not correlated to in-vitro data. In this study, an ex-vivo model was developed to evaluate the impact of ascorbic acid and tocopherol on the antioxidant capacity (AOC) of porcine skin. After that, the sensitivity of the method was evaluated using different antioxidants on skin and correlated to the in-vitro AOC experiments.

MATERIALS AND METHODS

Ascorbic acid and tocopherol were prepared in 1 - 30% (w/v) solutions, while Q10 was prepared at lower concentrations (0.5 - 5% (w/v)) and the in-vitro AOC was determined via ORAC assay [3]. Subsequently, the obtained solutions were applied on porcine skin, incubated for 2h at 32°C and tape stripping technique was done to remove the stratum corneum up to 30 layers. In the final step, the tapes were extracted with ethanol (70%), subjected to ORAC assay, and the skin AOC with and without treatment was determined.

RESULTS

The topical application of ascorbic acid and tocopherol increased the skin AOC to a maximum of 191% ± 32% for ascorbic acid (20%) and 130% ± 5% for tocopherol (30%). For the Q10 solutions, 0.5% improves the skin AOC to 126% ± 10% compared to the AOC of untreated skin. Afterwards, a linear decrease in skin AOC was observed upon the application of higher concentrations, down to 55% ± 7% for the 5% Q10. Thus, demonstrating a pro-oxidative effect of Q10 with concentrations > 0.5%. The correlation between in-vitro and ex-vivo AOC for Q10 reflected a significant (p=0.0069) inversed correlation with Pearson r of -0.9931.

CONCLUSION

This study successfully demonstrated the ability and the sensitivity of the ex-vivo model to determine the antioxidative and the pro-oxidative effect of topical antioxidant formulations on skin. The model is convenient and versatile for the determination of safe doses of antioxidants to be used in cosmetic formulations.

REFERENCES

PRODUCTION AND CHARACTERIZATION OF PETROLEUM JELLY NANOPARTICLES AND ITS OCCLUSION EFFECT ON SKIN

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INTRODUCTION

Petroleum jelly (PJ) is an extensively used ingredient in pharmaceutical and cosmetic formulations. However, its complex rheological behaviour in combination with high batch-to-batch variations represent a big hurdle for both formulation development and patient compliance [1,2]. To overcome this problem, in the study a new formulation approach – PJ nanoparticles (PJ-NP) were developed.

MATERIALS AND METHODS

The PJ-NP contained 10% (w/w) PJ, 1% (w/w) TPGS (d-α tocopheryl polyethylene glycol 1000 succinate) as stabilizer and purified water. The PJ-NP were produced by using high pressure homogenization and were characterized regarding their size, zeta potential (ZP) and rheological properties. In addition, the PJ-NP were applied onto skin of fresh porcine ears, to characterize their occlusive properties. TEWL and skin capacitance were measured with Tewameter TM 300 and Corneometer CM 825. Results were compared to pure PJ.

RESULTS

The PJ-NP possess a particle size of $221 \pm 5$ nm, a polydispersity index (PDI) of 0.102 and a ZP of $-12 \pm 1$ mV. The dispersions appear milk like and show Newtonian flow behaviour with excellent spreadability on skin. After dermal application, the PJ-NP formed a protection film on top of the skin. The TEWL and the skin capacitance measurements revealed that considerably lower amounts of PJ-NP were required to achieve the same occlusion effect compared to pure PJ. Thus, indicating a higher occlusion efficacy of PJ-NP than pure PJ. This finding could be explained by previously postulated improved adhesive properties of nanosized material [3].

CONCLUSION

In this study, PJ-NP were successfully produced. PJ-NP showed improved spreadability and increased occlusion properties compared to pure PJ. Future experiments will now focus on the development and characterization of drug loaded PJ-NP for improved dermal and transdermal drug delivery of lipophilic active compounds.

REFERENCES

INTRODUCTION

Curcumin has several beneficial pharmacological properties after dermal application. However, its use is limited due to its low water solubility and poor permeability (BCS class IV drug). A simple and efficient approach to overcome these obstacles could be the newly invented smartFilm-technology. This formulation enables the amorphous stabilization of actives into the pores of cellulose matrices, which leads to a higher solubility and dissolution velocity. As a result, dermal bioavailability might be improved in a skin-friendly manner without the use of a penetration enhancer [1, 2]. Therefore, the first step was to investigate the release kinetics of the curcumin using in-vitro diffusion studies. The second step was to challenge the performance of the smartFilms in an ex-vivo skin penetration experiment.

MATERIALS AND METHODS

The smartFilms were produced by adding an ethanolic curcumin solution onto printer paper cutouts. The crystalline state was determined by X-ray diffraction. The drug release was carried out with Franz diffusion cells at 32 °C for 24 h. The ex-vivo skin penetration studies were conducted on fresh porcine ears. The amount penetrated after 6 h was analyzed semi-quantitatively by observing the autofluorescence of curcumin in the skin.

RESULTS

X-ray diffraction indicated that all curcumin was loaded into the paper in amorphous state. The cumulative in-vitro permeation profile showed a delayed release with a lag time of about 2.7 h. This might result from the cellulose matrix, which needs to swell before the curcumin can be released. Afterwards, a linear release kinetic with a mass flux of 1.07 μg/cm2/h was observed. The ex-vivo skin penetration trial revealed an intense fluorescence even in the viable dermis, which indicates an efficient (trans-)dermal penetration of curcumin from the smartFilms. The improved solubility of the active led to an increased concentration gradient with enhanced passive diffusion into the skin.

CONCLUSION

This study revealed a linear release of curcumin from the smartFilms, which resulted in a pronounced transdermal penetration. SmartFilms are composed of commercially available paper and amorphous actives with no further skin-irritating excipients. With this, they can be regarded to be not only an effective but also a skin friendly dermal drug delivery system.

REFERENCES

NANOSTRUCTURED LIPID CARRIERS: BALANCE BETWEEN SKIN CARE AND PENETRATION EFFICACY

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INTRODUCTION
Nanostructured lipid carriers (NLC) are an advanced drug delivery system for dermal applications. Due to their nanometer sizes, they can adhere onto skin, creating a lipid film. This “invisible patch” strengthens the lipid barrier, increases skin hydration, and promotes the penetration of incorporated active ingredients (AI) [1]. The aim of this study was to define the optimal lipid concentration that is required for the formation of the “invisible patch” and thus for the most efficient penetration of the AI. Furthermore, since NLC are surrounded by emulsifiers, which can harm the skin’s lipid barrier and consequently can foster the dermal penetration, the second aim was to find a suitable stabilizer to keep the balance between skin care and penetration efficacy.

MATERIALS AND METHODS
The first part of the study was investigated with varying contents of the lipid phase (cetyl palmitate + Miglyol® 812) in the range of 5-40%, dispersed in 1% Plantacare® 818 (PLC). The second part was evaluated by using different stabilizers (all 1 %), i.e., PLC and soy lecithin (skin-friendly) and sodium dodecyl sulfate (SDS, non-skin friendly). A lipophilic fluorescent dye (Dil) was added to all formulations as surrogate for an AI. The dermal penetration efficacy was determined according to the method described in [1].

RESULTS
Findings of the first part resulted in a particle-depended penetration efficacy until a lipid content of 20 %. A further increase led to a plateauing penetration efficacy, due to a saturation of the skin surface with NLC (monolayer). The second part proved the influence of stabilizers on the penetration efficacy. NLC with the skin-barrier-disrupting SDS revealed the most pronounced penetration. In contrast, PLC as a large molecule, showed the least penetration for the AI. Lecithin achieved a sufficient penetration due to an increased fluidization of the skin’s lipid barrier [2]. Furthermore, its physiological composition makes it a particularly balanced stabilizer for drug delivery and skin care.

CONCLUSION
An ideal NLC-formulation to combine penetration efficacy and skin care can be realized by linking the optimal lipid particle concentration (20 %) with skin-friendly, but penetration promoting stabilizers (e.g., lecithin). This approach is known as advanced corneotherapy [1].

REFERENCES
LIPID NANOPARTICLES FOR PARTICLE-ASSISTED DERMAL PENETRATION ENHANCEMENT

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INTRODUCTION

A recently published study offered new insights into the dermal penetration mechanisms of suspensions and demonstrated that particles are connected to the skin via an aqueous meniscus [1]. Active compounds (AC) dissolved in the meniscus create a high local concentration gradient and cause an increased local penetration efficacy. So far, this effect has only been proven for nanosuspensions, where the AC is released from the carrier itself. However, in theory, any particle can be considered to form an aqueous meniscus on the skin. Thus, it can be assumed that the addition of particles to liquids that contain dissolved AC can improve the dermal penetration efficacy of the AC via the above-mentioned mechanism. The aim of this study was to prove this theory.

MATERIALS AND METHODS

Nanostructured lipid carriers (NLC) were used as particles. They consisted of cetyl palmitate and Miglyol® 812 (60/40(m/m)), stabilized with 1 % Plantacare® 818. The total lipid concentrations varied from 0, 5, 10, 20 and 40 %. 0.005 % fluorescein disodium salt was added to all formulations as surrogate for a hydrophilic AC. The dermal penetration efficacy was determined on the ex-vivo porcine ear model by using epifluorescence microscopy and digital image analysis [2].

RESULTS

Results demonstrated the capability of NLC to enhance the dermal penetration efficacy of the hydrophilic AC. The addition of 5 % lipid phase boosted the amount of the penetrated dye by approx. 85 % in comparison to the pure AC solution. By increasing the number of particles, this effect could be further enhanced. Therefore, the 40 % lipid concentration revealed the greatest improvement not only in terms of the total amount penetrated (+163 %) but also in terms of penetration depth (2.5x higher than the pure solution).

CONCLUSION

This study proved that the addition of particles to a topical formulation enhances the dermal penetration efficacy of dissolved active ingredients in the formulation. Particle-assisted penetration enhancement (PAPE) is a simple but highly efficient approach. It can be used for example to produce topical products with reduced amounts of AC and/or for the development of topical productions with tailor-made penetration profiles.

REFERENCES

INTRODUCTION

Tablets persist as the most common dosage form nowadays. The preferred process of their preparation is direct compression. The crucial step in the process is mixing, which can be described as a transfer of particles relative to each other until the maximum level of disorder is achieved [1]. The blend for direct compression does not undergo extensive process steps (like the creation of interactive mixtures during wet granulation) so high levels of homogeneity are necessary. Therefore, specific strategies, such as subdividing the mixing into multiple steps and introducing sieving before each one of them, are being adopted in industrial practice. Presented work deals with a mixture intended for direct compression, where some specific mixing strategy is necessary. The objective is to examine and describe different mixing strategies consisting of different steps, compare them according to resulting homogeneity and process complexity and recommend the ideal process for industrial use.

MATERIALS AND METHODS

Experiments were performed on a model mixture having 5.6 % drug loading. It consisted of a placebo (excipient mixture) and a specific drug (bisoprolol) batch with a specific particle morphology (small, needle-like crystals), which is quite problematic in direct tablet compression. The tested mixing processes consisted of a different number of mixing steps, some with preceding sieving, performed on Turbula T2F 3D-mixer.

RESULTS

The sieving before the mixing step itself proved crucial during the experiments. However, it turned out that it is not necessary to perform it before each step. It has a significant role mostly in the first step (out of 1 – 3), where the drug is added. An alternative consisting of only two steps and one sieving showed promising results (final mixtures' coefficient of variation $CV = 2.81\%$) comparable to the original process ($CV = 2.36\%$).

CONCLUSION

As the sieving step is usually quite time-consuming in the industry, alternatively to the commonly used approach of placing the sieving before each one of the mixing steps, a quality by design approach was demonstrated to identify the necessary critical steps and adjust the mixing process strategy. Its incorporation into the industrial practice could significantly streamline the model mixture preparation and it can be adopted as a profiling approach to prevent overdesigning in the newly developed direct compression processes.

REFERENCE

INVESTIGATION OF SURFACE MODIFIED MESOPOROUS SILICAS LOADED WITH AN ANTIPARKINSONIAN ACTIVE SUBSTANCE

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INTRODUCTION

The levodopa methyl ester hydrochloride (LDME) is a derivative of levodopa possessing several advantages in per os formulations compared to levodopa, like more rapid absorption, less apparent drug accumulation, less inter-patient variability [1]. Our aim was to regulate the release of the LDME to treat the off periods of Parkinson’s disease.

MATERIALS AND METHODS

In the first part of our work, the hydrophobization reaction was performed. 0.20 g of mesoporous silica powder was dispersed in 20 mL n-hexane, the concentration of the chloro(trimethyl)silane (CTMS) – the hydrophobization agent – was 10 mM and 20 mM. Each reaction lasted for 2 hours at 25 °C. The hydrophobized silicas were characterized by contact angle measurement, mid-infrared spectroscopy, and charge titration. Thereafter the LDME was incorporated into the silica using a rotary evaporator based on 32 factorial design (varying factors: the hydrophobization extent, the LDME:excipient ratio). The dissolution tests were performed at 37 °C, pH=6.8. The drug content, the amorphization extent of the products, the secondary interactions, and the in vitro release properties were measured. The release tests were monitored by high-performance liquid chromatography.

RESULTS

In the case of 10 mM of CTMS, the contact angle measured with water was below 90°, besides 20 mM reagent resulted in higher contact angle. 5-20 % w/w of LDME was was homogeneously distributed in amorphous form in the mesoporous silica. The release rate of the LDME could be controlled by silylating the silica. The release of LDME was retarded with 1.3-79-fold compared to reference which was considered significant in the most cases.

CONCLUSION

LDME containing products were formulated and the drug release rate was controlled. The ones with immediate-release can be capable of achieving quick onset. The ones with slower release can provide constant blood level.

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REFERENCES

DYNAMIC COMPACTION ANALYSIS OF LIQUISOLID SYSTEMS WITH MAGNESIUM ALUMINOMETASILICATE AS CARRIER

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INTRODUCTION

Development of novel porous excipients with high specific surface area enabled formulation of liquisolid systems with considerably increased content of liquid drug (or drug solution/suspension) in comparison to those prepared with commonly used carriers, such as microcrystalline cellulose, while ensuring good flowability. However, liquisolid tablet manufacturing would require these powders to have both good flowability and good compaction properties. Tableting of liquisolid systems has been recognized as highly challenging, but studies addressing this issue are still scarce [1, 2]. The aim of this study was to investigate the influence of formulation factors, carrier to coating ratio (R) and liquid load (Lf), on flowability and compaction properties of liquisolid systems prepared with Neusilin® US2 as carrier. The influence of pre-compression force application on compaction properties was also tested.

MATERIALS AND METHODS

Neusilin® US2 (Fuji Chemical Industry Co, Ltd, Japan) was used as a carrier, colloidal silicon dioxide as a coating agent and polyethylene glycol 400 as a liquid phase. The admixtures were prepared using mortar and pestle, in three carrier to coating ratios (10, 20 and 30) with concentration of the liquid phase ranging between 38.9% and 55.7%. Flow rate was determined using Erweka flowmeter type GDT. Carr index and Hausner ratio were calculated from bulk and tapped density (STAV 2003 jolting volumeter). Dynamic compaction analysis was performed using Gamlen D series compaction analyser. Compact resistance to crushing was determined using Erweka TBH 125H and tensile strength was calculated.

RESULTS

The results obtained showed that carrier to coating ratio had a less pronounced influence on both flowability and compaction properties than liquid load. All of the admixtures showed acceptable flowability, with Carr’s index values ranging between 11 and 18%. Good tabletability was achieved with Lf values up to 1.0. In the case of admixtures with Lf values higher than 1.0, formation of compacts was possible only at lower compression pressures. Namely, at higher compression pressures pronounced sticking and squeezing out of these admixtures from the tablet die was observed. Liquisolid systems with lower liquid content were more susceptible to elastic deformation, with all of the investigated admixtures showing relatively high values of elastic recovery (25 to 45%). Detachment stress was relatively low for all of the investigated admixtures, but interestingly ejection stress values were rather high (above 5 MPa). With the increase in liquid content, the values of ejection stress decreased, but were still relatively high. The application of pre-compression force did not show notable effect on the compaction properties of liquisolid admixtures.

CONCLUSION

The results obtained indicate that Neusilin® US2 could be used as a suitable carrier in formulation of liquisolid tablets with high liquid content. The admixtures prepared showed both good flowability...
and good compaction properties at high liquid content (up to 49%). The relatively high ejection stress values indicate that the addition of lubricant might be needed.

ACKNOWLEDGEMENT

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REFERENCES

INTRODUCTION

HRT is often used by postmenopausal women. In contrast to contraception, HRT – due to possible adverse effects – should not be administered via the oral route but should be applied via transdermal patches or creams. The hormone dose required is individual and thus requires individual prescription. The preparation of HRT creams is not standardized. Consequently, various cream bases are prescribed and used for the compounding of individual HRT preparations. So far, no data is available on the influence of vehicle on dermal penetration of hormones for HRT. Thus, a prediction of the pharmacokinetic profile and/or possible differences between the different HRT creams is not possible. Therefore, in this study, different HRT creams were produced and differences in the dermal and transdermal penetration profiles were determined in an ex vivo skin model.

MATERIALS AND METHODS

The lipophilic, fluorescent dye Dil was used as hormone surrogate and was incorporated into 15 different vehicles. The formulations were applied on fresh porcine ears and the penetration was determined from 20 μm vertical cuts from the skin biopsies with epifluorescence microscopy and subsequent digital image analysis [1].

RESULTS

The different vehicles showed pronounced differences in the penetration efficacy of the hormone surrogate (HS). Basis cream DAC - a common vehicle in the compounding pharmacy was used as benchmark control. The mean penetration depth (MPD) of the HS from this vehicle was 72 μm, indicating an effective transdermal penetration of the HS. The MPD form other vehicles ranged from 18 μm (-75%) to 194 μm (+170%). Also, the total amounts penetrated (TAP) were affected by the type of vehicle. The vehicle with least efficient penetration resulted in a 33% lower TAP when compared to the benchmark control and the best penetrating formulation increased the TAP to 160%. The improved penetration is due to ingredients with skin moisturizing properties, e.g., glycerol or hyaluronic acid.

CONCLUSION

The vehicle strongly affects the penetration efficacy of the hormones. Therefore, not only individual hormone doses but also standardized formulation principles are required to ensure efficient, predictable and safe HRT with transdermal HRT creams.

REFERENCES

TECHNOLOGY OF SUBCRITICAL CO2 EXTRACTION TO PRODUCE A SOFT EXTRACT FROM DENDROSTELLERA STACHYOIDES

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INTRODUCTION

The relevance of the study lies in the fact that the flora of the Republic of Kazakhstan has the richest reserves of plant resources, in this regard of great theoretical and practical interest are wild plants of the family Thymelaeaceae (Thymelaceae), which are widely distributed in Kazakhstan. The studied plants of this family possess a wide spectrum of pharmacological, including antioxidant, antibacterial, antitumor, antimetastatic activity. Most of them contain diterpenes, flavonoids and polysaccharides. Extraction of herbal material with CO2 is a method to improve yield of extraction for specific active components. In contrast to the more common supercritical extraction the use of subcritical CO2 extraction has not been intensively studied yet. The advantages of this pre-critical CO2 extraction technology include low energy consumption, environmental friendliness, ease of operation and the relatively low cost of manufacturing hardware. The aim of the study was obtain a soft extract from the plant Dendrostellera stachyoides using a subcritical CO2 extraction and to determine its the qualitative composition.

MATERIALS AND METHODS

The above-ground parts of the plant Dendrostellera stachyoides were harvested in the flowering stage. The plant was dried at 250°C and ground using a mill. Then the material was subjected to subcritical CO2 extraction under the following conditions: T=19-22 0C, P=45-52 atm, t=13 hours. The extract was analysed with GC-MS apparatus (Agilent 6890N/5973N). The separation was performed using a DB-WAXetr 30 m long, 0.25 mm inner diameter and 0.25 μm film thickness capillary column at a constant carrier gas speed (helium) of 1 ml/min. The chromatography temperature was programmed from 40 °C (10 min exposure time) at a heating rate of 5 °C/min to 270 °C (10 min exposure time). The detection was done in SCAN mode m/z 34-750. Wiley 7th edition and NIST'02 libraries were used to decipher the obtained mass spectra.

RESULTS

A soft extract of dark brown color, with a specific odor was obtained. 46 substances were identified by GC-MS analysis. High content of the following compounds was determined in the extract: 2(1H)-naphthalenone, 7-ethynyl-4a,5,6,7,8,8a-hexahydro-1,4a-dimethyl-, (1α,4aβ,7β,8aα)-29.22%, longipinocarveol, trans-12.88%, 1-oxaspiro[2.5]octane, 5,5-dimethyl-4-(3-methyl-1,3-butadienyl)-8.4%, isoaromadendrene epoxide-5.18%, benzyl benzoate-3.7%.

CONCLUSION

A soft extract has been obtained by pre-critical CO2 extraction. High content of the compounds which exhibit antibacterial, antipediculosis and antioxidant activity was determined in the extract. A dosage form with antibacterial activity is planned. The work to isolate the biologically active complex from the plant under study continues.
FACTORIAL DESIGN-BASED LIPOSOME OPTIMISATION APPLYING VESICLE-MODIFYING MEMBRANE ADDITIVES

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INTRODUCTION

Liposomes are one of the core points of pharmaceutical research; however, some topics still need to be specified in the field. An adequate surface charge is indispensable to maintain the stability of the vesicles. Samples with minimum ±30 mV zeta potential are considered stable [1]. The charge of the phospholipid double bilayer can be modified with different additives. The present study was designed to optimise, investigate, and characterise liposomal formulations made with charge imparting agents such as dicetylphosphate (DCP) or stearylamine (SA) [2, 3].

MATERIALS AND METHODS

The optimised formulations were determined by following the settings of the fractional factorial design. The liposomes were prepared via the thin-film hydration method from different ratios of phosphatidylcholine, cholesterol, and membrane additives (DCP or SA), then freeze-dried for storage issues. Mean vesicle size, size distribution, and zeta potential values were evaluated. Furthermore, the structure of liposomes, interactions between the membrane elements, and the thermostability of the samples were investigated in the case of the developed systems.

RESULTS

The characterisation of the optimised DCP- or SA-containing nanoparticles demonstrated zeta potentials higher than 30 mV in absolute value, indicating stable formulations, vesicles under 150 nm, and narrow polydispersity indexes. TG and DSC analysis showed no mass changes above 250°C. Spherical vesicle forms were detected from the TEM images.

CONCLUSION

The factorial design-based study plans led to experimentally proved zeta potential-optimised, stable liposomes in parallel with a practical knowledge base about the impact of the DCP and the SA ratios on the quality of the liposomes.

REFERENCES


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