Technische Universität Braunschweig

pvz Zentrum für Pharmaverfahrenstechnik

5th International Symposium on Pharmaceutical Engineering Research

SPhERe

CONFERENCE PROGRAMME

18 – 20 October 2023

CONFERENCE EDITION

TU Braunschweig • Center of Pharmaceutical Engineering

Welcome Note

It is our pleasure to welcome you to the *5th International Symposium on Pharmaceutical Engineering Research – SPhERe*. The conference has established as an international platform for exchange of activities and ideas on pharmaceutical engineering research. We are delighted that, after a virtual meeting 2021 in the midst of the Corona pandemic, we today can meet in person at TU Braunschweig.

SPhERe addresses major topics of cutting-edge processes and methods for the cost-effective development of innovative and customized drugs. Bringing together pharmacists, process engineers, production engineers and microtechnologists from academia and industry provides a forum for discussion of perspectives between representatives of different research disciplines, thereby strengthening the community of pharmaceutical engineering and related fields.

The oral and poster presentations of SPhERe 2023 include API synthesis, scale up/scale down processes, solid dosage forms, semi-solid and liquid dosage forms, digital models in pharmaceutical manufacturing, analytics/PAT, and microsystems for pharmaceutical testing. Two key note lectures deal with engineering aspects of bringing API production to Germany and pharmaceutical engineering at nanoscale exemplified by RNA delivery.

A strong focus is on involving early career researchers. The poster session is preceded by brief oral presentations of the individual posters. In addition, there is a distinctive career session, and a special guest lecture focuses on EU funding and policies for research and innovation as a companion for a research career.

The conference takes place at the Center of Pharmaceutical Engineering (PVZ) of TU Braunschweig. This interdisciplinary research center offers a unique environment for scientists devoted to the advancement of pharmaceutical engineering.

We welcome you to SPhERe 2023 and wish you interesting talks and exciting discussions.

Prof. Dr.-Ing. Stephan Scholl
Conference Chair SPhERe 2023

Prof. Dr. Ludger Beerhues
Conference Co-Chair SPhERe 2023

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CONFERENCE DAY 1 • 18 OCTOBER 2023

10:00 Check-In

11:30 **OPENING**
Opening by Stephan Scholl, Conference Chair, TU Braunschweig
Welcome address by Knut Baumann, Vice President for Academic and Student Affairs, TU Braunschweig

KEYNOTE LECTURE
Chair: Stephan Scholl

11:45 **How to bring API production to Germany? - Engineering Aspects**
Michael Häberl, Merck Life Science KGaA, Darmstadt, Germany

12:30 Lunch Break

SESSION I: API Synthesis
Chair: Ludger Beerhues

13:30 **INVITED LECTURE**
New approaches for targeting the intracellular allosteric binding site of GPCRs
Matthias Schiedel, Institute of Medicinal and Pharmaceutical Chemistry, TU Braunschweig, Germany

13:55 **Heading to phase I – Scale up of the production process of the antibiotic candidate corallopyronin A into industrial scale**
Miriam Große[2,8], Birthe Sandargo[2,8], Rolf Jansen[2,8], Tim Becker[3], Anna Krome[3], Andrea Schiefer[1,7], Silke Alt[6], Rolf Müller[5], Thomas Hesterkamp[6], Kenneth Pfarra[7], Karl Wagner[3,7], Marc Stadler[2,8], Achim Hoerauf[1,7]
[1]Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn; [2]Department Microbial Drugs, Helmholtz Centre for Infection Research, Braunschweig; [3]Department of Pharmaceutical Technology and Biopharmaceutics, University of Bonn; [4]Institute for Pharmaceutical Biology, University of Bonn; [5]Department Microbial Natural Products, Helmholtz Institute for Pharmaceutical Research Saarland; [6]Translational Project Management Office (TPMO), German Center for Infection Research; [7]German Center for Infection Research (DZIF), Partner Site Bonn-Cologne; [8]German Center for Infection Research (DZIF), Partner Site Hannover-Braunschweig

14:10 **Mycelial pellets - an intertwined matter: How salt-enhanced cultivation affects product formation and filamentous cellular morphology**
Zuzanna J. Kozanecka[1,2], Jule Muehlenbrock[1,2], Detlev Rasch[1,2], Rainer Krull[1,2]
[1]Institute of Biochemical Engineering, TU Braunschweig, Germany; [2]Center of Pharmaceutical Engineering, TU Braunschweig, Germany

14:25 **Unveiling the biosynthesis of hyperforin and its analogues for engineering strategies**
Hesham MB Sayed[1,2], Tomke Meents[1,2], Sara Nassar[1,2], Benye Liu[1,2], Ludger Beerhues[1,2], Islam El-Awaad[1,2]
[1]Institute of Pharmaceutical Biology, TU Braunschweig, Germany;
[2]Center of Pharmaceutical Engineering (PVZ), TU Braunschweig, Germany

14:40 **INVITED LECTURE**
Manufacturing through plant cell culture technology – sustainable, controlled and flexible in scale
Gilbert Gorr, Phyton Biotech GmbH, Ahrensburg, Germany

15:05 Bio Break

SESSION II: SCALE-UP / SCALE-DOWN PROCESSES

Chair: **Rainer Krull**

15:20 **INVITED LECTURE**
Towards sustainable continuous production of crystalline APIs
Kerstin Wohlgemuth, Laboratory of Plant and Process Design, TU Dortmund, Germany

15:45 **Scaling up crystallization conditions for achieving targeted crystal morphologies of an active pharmaceutical ingredient**
Nicolás Ramos[1], Matthias Kind[1]
[1]Karlsruhe Institute of Technology, Germany

16:00 **Comparability of tablet compression characterization in small- and full-scale production**
Doreen Dunst[1], Rebecca McVicker[2], Ina Petry[1]
[1]Fette Compacting GmbH, Schwarzenbek, Germany; [2]Tableting Ltd., Nottingham, UK

16:15 **Multiscale morphology engineering for rebeccamycin production with the filamentous actinomycete Lentzea aerocolonigenes**
Anna Dinius[1,3], Marcel Schrader[2,3], Katharina Mohrdieck[1], Arno Kwade[2,3], Rainer Krull[1,3] [1]Institute of Biochemical Engineering, TU Braunschweig, Germany, [2]Institute for Particle Technology, TU Braunschweig, Germany; [3]Center of Pharmaceutical Engineering, TU Braunschweig, Germany

16:30 **INVITED LECTURE**
A robotic- and AI-assisted accelerated tablet formulation and process design platform
Daniel Markl, Centre for Continuous Manufacturing and Advanced Crystallisation (CMAC), Strathclyde Institute of Pharmacy and Biomedical Sciences, Glasgow, UK

16:55 Bio Break

POSTER SESSION

Chair: **Islam El-Awaad**

17:15 Poster Short Talks

18:15 Poster Party

20:30 END OF DAY

CONFERENCE DAY 2 • 19 October 2023

08:00 Check-In

KEYNOTE LECTURE
Chair:

08:30 **Pharmaceutical Engineering at Nanoscale: Delivery of RNA and more**
Heinrich Haas, Department of Biopharmaceutics and Pharmaceutical Technology, Johannes Gutenberg-Universität, Mainz, Germany

SESSION III: SOLID DOSAGE FORMS
Chair: Denise Steiner

09:15 **INVITED LECTURE**
Material characterization in drug product development of oral solid dosage forms – an industry perspective
Carolin Riehl[1], Lena Mareczek[1], Meike Harms[1], Stephan Reichl[2]
[1]Merck Healthcare KGaA, Darmstadt, Germany; [2]Institute of Pharmaceutical Technology and Biopharmaceutics, TU Braunschweig, Germany

09:40 **Loading of oily ink formulations on structured orodispersible film templates for patient individual drug dosing**
Lena Mahlberg[1], Denise Steiner[1]
[1]University of Tübingen, Department of Pharmaceutical Technology, Germany

09:55 **Damaging mechanism of functionally coated pellets in tableting machines and damage mitigation**
Luisa Enders[1,2], Lara Stein[1,2,3], Gernot Warnke[3], Jan Henrik Finke[1,2]
[1]Institute for Particle Technology, TU Braunschweig, Germany; [2]Center of Pharmaceutical Engineering (PVZ), TU Braunschweig, Germany, [3]JRS PHARMA GmbH & Co. KG, Rosenberg, Germany

10:10 **Manufacturing and characterization of particle-based silica aerogels for pharmaceutical applications**
Jennifer Pierick[1,2], Lisann Soldanski[1,2], Anne Jupitz[1,2], Georg Garnweitner[1]
[1]Institute for Particle Technology (iPAT), TU Braunschweig, Germany; [2]Center of Pharmaceutical Engineering (PVZ), TU Braunschweig, Germany

10:25 **Tableting of living microorganisms: Influence of biomass concentration in fluidized bed granules on physical-mechanical and microbiological tablet properties**
Karl Vorländer[1,2], Arno Kwade[1,2], Jan Henrik Finke[1,2], Ingo Kampen[1,2]
[1]Institute for Particle Technology, TU Braunschweig, Germany; [2]Center of Pharmaceutical Engineering (PVZ), TU Braunschweig, Germany

10:40 Discussion

10:45 Bio Break

SESSION IV: SEMI-SOLID & LIQUID DOSAGE FORMS
Chair: Heike Bunjes

11:00 **INVITED LECTURE**
Current trends in dermal and transdermal drug delivery
Jarmila Zbytovská, University of Chemistry and Technology Prague, Faculty of Organic Technology, Prague, Czech Republic

11:25 **Quantum dots nanoemulsion as a fluorescent tool for labeling zebrafish cells to study neurodegenerative diseases**
Luiza Araújo Gusmão[1], Antonio Claudio Tedesco[2], Reinhard W. Köster[1]
[1]Zoological Institute, Cellular and Molecular Neurobiology, TU Braunschweig, Germany; [2]University of São Paulo, Ribeirão Preto, Brazil

11:40 **Controlled release from lipid nanoparticles by modification of drug lipophilicity**
Nina Baumann[1,2], Janosh Baumgarten[2,3], Conrad Kunick[2,3], Heike Bunjes[1,2]
[1]Institute of Pharmaceutical Technology and Biopharmaceutics, TU Braunschweig, Germany; [2]Center of Pharmaceutical Engineering (PVZ), TU Braunschweig, Germany; [3]Institute of Medicinal and Pharmaceutical Chemistry, TU Braunschweig, Germany

11:55 **High-pressure production of nanoemulsions using nickel-based superalloy membranes**
Daniel Jupke[1,2], J. M. Lück[3], C. Heidenreich[2,4], Heike Bunjes[2,4], J. Rösler[3], Jan-Henrik Finke[1,2], Arno Kwade[1,2]
[1]Institute for Particle Technology, TU Braunschweig, Germany; [2]Center of Pharmaceutical Engineering (PVZ), TU Braunschweig, Germany; [3]Institute for Materials Science, TU Braunschweig, Germany; [4]Institute of Pharmaceutical Technology and Biopharmaceutics, TU Braunschweig, Germany

12:10 **Bioprocess characterisation with microfluidic Devices**
Marco P.C. Marques, Nicolas Szita,
University College London (UCL), Department of Biochemical Engineering London, WC1E 7JE, United Kingdom

12:25 Discussion

12:30 Lunch Break

SESSION V: DIGITAL MODELS IN PHARMACEUTICAL MANUFACTURING

Chair: Stephan Scholl

14:00 **INVITED LECTURE**
Process analytical technologies for inline control of fluidized bed agglomeration using artificial intelligence
Michael Jacob, Marcel Voisin; Glatt Ingenieurtechnik GmbH, Weimar, Germany

14:25 **In-silico supported methods (COSMO-RS) for the sustainable and targeted extraction and isolation of natural products from side-streams of wine production**
Mats Kiene[1], Hendrik Fellensiek[1], Malte Zaremba[1], Gerold Jerz[1], Edwin Januschewski[2], Andreas Juadjur[2], Peter Winterhalter[1]
[1]Institute of Food Chemistry, TU Braunschweig, Germany; [2]German Institute of Food Technology, Quakenbrück, Germany

14:40 **Development of a method for AI supported crystallization process control**
Conrad Meyer[1], Stephan Scholl[1]
[1]Institute for Chemical and Thermal Process Engineering, TU Braunschweig, Germany

14:55 **Learning adsorption processes with physics-informed neural networks: a parameter sensitivity perspective**
Md Meraj Khalid[1], Subiksha Selvarajan[1], Caroline Heiduk[2], Stephan Scholl[2], René Schenkendorf[1]
[1]Automation & Computer Sciences Department, Harz University of Applied Sciences, Wernigerode, Germany; [2]Institute for Chemical and Thermal Process Engineering, TU Braunschweig, Germany

15:10 **Perspectives of Work in Pharmaceutical Production**
Hans-Walter Hoehl, University of Applied Science BFI, Vienna, Austria

15:25 Discussion

15:30 Bio Break

SPECIAL GUEST SESSION

Chair: Stephan Scholl

15:45 **EU Funding & Policies for Research and Innovation: A Companion for a Research Career**
Inga Benner, European Liaison Office of the German Research Organisations (KoWi), Bonn, Germany

16:45 END OF DAY

19:00 Conference Dinner Dornse

CONFERENCE DAY 3 • 20 OCTOBER 2023

08:00 Check-In

CAREER SESSION

Chair: Gerlinde Benninger / Denise Steiner

08:30 *Kerstin Wohlgemuth, TU Dortmund, Germany*
Jhinuk Rahman-Yildir, NextPharma, Göttingen, Germany

10:00 Bio Break

SESSION VI: ANALYTICS, PAT

Chair: Andreas Dietzel

10:15 **INVITED LECTURE**
Benefits of using UV-Vis, NIR and Raman spectrometers as inline PAT in pharmaceutical application
Fuat Eker, Andreas Berghaus; ColVisTec AG, Berlin, Germany,

10:40 **Online coupling of size exclusion chromatography to Raman spectroscopy for protein analysis**
Jana Thissen[1,2], Martin D. Klaßen[1], Michael C. Hacker[2], Jörg Breitkreutz[2], Thorsten Teutenberg[1], Björn Fischer[2]
[1]Institut für Umwelt & Energie, Technik & Analytik e.V. (IUTA), Duisburg, Germany; [2]Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Düsseldorf, Germany

10:55 **Emerging PAT for freeze-drying processes for advanced process control**
Alex Juckers[1,2], Petra Knerr[2], Frank Harms[2], Jochen Strube[1]
[1]Clausthal University of Technology, Clausthal-Zellerfeld, Germany; [2]Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany

11:10 **A-TEEM spectroscopy for fast and efficient QC and PAT of liquid samples**
Sascha Just, HORIBA Scientific, Oberursel, Germany

11:25 ***In-situ characterization of cells in a bioreactor by ultrasound enhanced in-line Raman and ATR-FTIR spectroscopy***
Christoph Gasser, Stefan Schöller, Stefan Radel, usePAT GmbH, Vienna, Austria

11:40 Lunch Break

SESSION VII: MICROSYSTEMS FOR PHARMACEUTICAL TESTING

Chair: Iordania Constantinou

12:15 **INVITED LECTURE**
Droplet-based microfluidic screening: from basics to precision oncology
Doris Heinrich, Institut für Bioprozess- und Analysenmesstechnik e.V. (iba), Heilbad Heiligenstadt, Germany

12:40 **Development of an automated and fully sensor equipped capillary-wave microbioreactor for biopharmaceutical research**
Kevin Viebrock[1,4], Sven Meinen[2,4], Dominik Rabl[3], Detlev Rasch[1,4], Torsten Mayr[3], Andreas Dietzel[2,4], Rainer Krull[1,4]
[1]Institute of Biochemical Engineering, TU Braunschweig, Germany; [2]Institute of Microtechnology, TU Braunschweig, Germany; [3]Institute of Analytical Chemistry and Food Chemistry, TU Graz, Austria; [4]Center of Pharmaceutical Engineering (PVZ), TU Braunschweig, Germany

12:55 **Advances towards live-cell imaging on cell-stretching devices**
David Jaworski[1], Lara Hundsdorfer[2], Effie Bastounis[2], Iordania Constantinou[1]
[1]Institute of Microtechnology (IMT), Center of Pharmaceutical Engineering (PVZ), Technische Universität Braunschweig, Germany; [2]Institute of Microbiology and Infection Medicine (IMIT), Eberhard Karls University of Tübingen, Germany

13:10 **Overcoming oxygen impermeability in PDMS-free organ-on-a-chip devices with nanoporous plastics**
Franziska Buck[1], Jeroen. Bugter[1], Stephanie Fuchs[2], Torsten Mayr[2], Thomas E. Winkler[1]
[1]Institute of Microtechnology, TU Braunschweig, Germany; [2]Technische Universität Graz, Austria

13:25 **Real-time monitoring of cell confluence and barrier integrity of an endothelial monolayer on an ultrathin nanoporous membrane with a bioimpedance sensor.**
Bo Tang[1,3], Victor Krajka[1,3], Wei Zhao[1], Gazal Gökkus[1,3], Stephan Reichl[2,3], Iordania Constantinou[1,3], Andreas Dietzel[1,3]
[1]Institute of Microtechnology, TU Brauschweig, Germany; [2]Institute of Pharmaceutical Technology and Biopharmaceutics, TU Braunschweig, Germany; [3]Center of Pharmaceutical Engineering (PVZ), TU Braunschweig, Germany

13:40 Discussion

13:45 SPhERe 2023 POSTER AWARDS

Remarks & Conclusions

5th International Symposium on Pharmaceutical Engineering Research – SPhERe

18 – 20 October 2023

Poster Session – Detailed Programme

A dedicated poster session is preceded by an introductory presentation. Please note that your presentation time is limited to 2 minutes per poster. The detailed poster programme below lists only the presenting authors and their affiliations.

WEDNESDAY, 18 OCTOBER 2023

17:15 **Short Introduction by Islam El-Awaad**

17:18 P-I: API Synthesis

P-I.1 BIPHASIC BIOCATALYTIC TESTOSTERONE DEHYDROGENATION IN MICROFLUIDIC DROPLETS AND SLUG FLOW SYSTEMS
L. Xiang, Institute of Microtechnology, Center of Pharmaceutical Engineering, TU Braunschweig

P-I.2 ENGINEERING YEAST FOR PRODUCTION OF POLYPRENYLATED BENZOPHENONES AND XANTHONES
R. Mögenburg, Institute of Pharmaceutical Biology, Center of Pharmaceutical Engineering, TU Braunschweig

P-I.3 POLYMERIC IONIC LIQUIDS (PILs)-BASED HYDROGELS AS IMMOBILIZATION MATERIAL IN CATALYTIC REACTORS
F. M. Teubner, Institute for Chemical and Thermal Process Engineering, Center of Pharmaceutical Engineering, TU Braunschweig

P-I.4 GENERATION OF NOVEL PRISTINAMYCIN DERIVATIVES BY MUTASYNTHESIS
Juan Pablo Gomez-Escribano, German Collection of Microorganisms and Cell Cultures, Leibniz Institute DSMZ

17:26 P-II: Scale-Up / Scale-Down Processes

P-II.1 DEVELOPING A BIOCATALYTIC MULTIPHASE REACTION SCALE-DOWN MODEL
G. Schultz, Institute of Biochemical Engineering, Center of Pharmaceutical Engineering, TU Braunschweig

P-II.2 PICKING MICROORGANISMS BY IMPEDANCE FLOW CYTOMETRY
M. Mozafari, Institute of Microtechnology, TU Braunschweig

P-II.3 DEVELOPMENT AND SCALE-UP OF A MODIFIED RELEASE BILAYER TABLET BASED ON COMPACTION SIMULATION
Friederike Gütter, KORSCH AG

17:32 P-III: Solid Dosage Forms

P-III.1 PRODUCTION OF SELF-DISPERSIBLE LIPID PELLETS BY JETCUTTING
J. Pfeifer, Institute of Pharmaceutical Technology and Biopharmaceutics, Center of Pharmaceutical Engineering, TU Braunschweig

P-III.2 PREPARATION OF SELF-DISPERSIBLE PELLETS BY EXTRUSION-SPHERONIZATION
P. Schlosser, Institute of Pharmaceutical Technology and Biopharmaceutics, Center of Pharmaceutical Engineering, TU Braunschweig

P-III.3 SYSTEMATIC EVALUATION OF THE INFLUENCE OF MATERIAL PROPERTIES AND PUNCH COATINGS ON STICKING
I. Bialuch, Fraunhofer Institute for Surface Engineering and Thin Films IST, Center of Pharmaceutical Engineering, TU Braunschweig

P-III.4 CONTINUOUS RING LAYER GRANULATION IN A NEW LAB SCALE PLANT
Jan-Henrik Finke, Institute for Particle Technology, Center for Pharmaceutical Engineering, TU Braunschweig

17:40 P-IV: Semi-Solid & Liquid Dosage Forms

P-IV.1 DIFFERENTIAL SCANNING CALORIMETRY (DSC) STUDIES ON THE CRITICAL MICELLE TEMPERATURE (CMT) OF POLOXAMERS IN AQUEOUS SOLUTIONS AND LIPID NANO-EMULSIONS
O. Sukhbat, Institute of Pharmaceutical Technology and Biopharmaceutics, TU Braunschweig

P-IV.2 COMPARING PHYSICO-CHEMICAL CHARACTERISTICS OF NANOPOROUS SUPERALLOY MEMBRANES WITH THOSE OF MEMBRANES ESTABLISHED IN PREMIX MEMBRANE EMULSIFICATION
C. Heidenreich, Institute of Pharmaceutical Technology and Biopharmaceutics, Center of Pharmaceutical Engineering, TU Braunschweig

P-VI.3 EVALUATION OF TEMPERATURE EXPOSURE OF NANOPARTICLES DURING SPRAY DRYING
I. Klein, Department of Pharmaceutical Technology, University of Tübingen

17:46 P-IV: Digital Models in Pharmaceutical Manufacturing

P-V.1 PREDICTION OF SOLVATION FREE ENERGIES FOR ORGANOMETALLIC COMPOUNDS VIA MOLECULAR DYNAMICS SIMULATIONS
M. Sprick, Institute of Thermodynamics, Center of Pharmaceutical Engineering, TU Braunschweig

17:48 Analytics, PAT

P-VI.1 MICROELECTRODE MEASUREMENTS AND MODELLING OF OXYGEN CONSUMPTION PARAMETERS IN FILAMENTOUS PELLETS OF ASPERGILLUS NIGER
A. Dinius, Institute of Biochemical Engineering, Center of Pharmaceutical Engineering, TU Braunschweig

P-VI.2 IMPROVING IN-LINE MEASUREMENTS OF MODEL CRYSTALLIZATIONS BY THE CAREFUL APPLICATION OF AN ULTRASONIC STANDING WAVE
S. Radel, usePAT GmbH, Vienna, Austria

17:52 Microsystems for Pharmaceutical Testing

P-VII.1 ESTABLISHMENT OF A CAPILLARY WAVE MICROBIOREACTOR PLATFORM TO PERFORM PHAGOGRAMS
K. Viebrock, Institute of Biochemical Engineering, Center of Pharmaceutical Engineering, TU Braunschweig

P-VII.2 MODULATING EXTRACELLULAR MATRIX PROPERTIES IN ORGAN-ON-CHIPS
H. Kutluk, Institute of Microtechnology, Center of Pharmaceutical Engineering, TU Braunschweig

P-VII.3 ESTABLISHING A METHOD FOR QUANTIFICATION OF MUCUS IN CELL CULTURE MODELS OF NASAL MUCOSA
L. Klintz, Institute of Pharmaceutical Technology and Biopharmaceutics, Center of Pharmaceutical Engineering, TU Braunschweig

P-VII.4 GAP JUNCTION-MEDIATED CELL-CELL COMMUNICATION THROUGH ULTRA-THIN; ULTRA-POROUS BARRIER-CHIP MEMBRANES
J. Bugter, Institute of Microtechnology, Center of Pharmaceutical Engineering, TU Braunschweig

P-VII.5 OCULAR DYNAMITES – A MICROFLUIDIC MODEL OF THE HUMAN CORNEA FOR PRE-CLINICAL TESTING OF OPHTHALMIC DRUGS
V. Ledwig, Institute of Pharmaceutical Technology and Biopharmaceutics, Center of Pharmaceutical Engineering, TU Braunschweig

P-VII.6 AN IN VITRO MODEL OF MECHANICAL STRAIN ENHANCES CELLULAR UPTAKE OF SINGLE-WALLED CARBON NANOTUBES
David Jaworski, Institute of Microtechnology, Center of Pharmaceutical Engineering, TU Braunschweig

18:04 End of Poster Introductory Presentation

Poster Exhibition

The poster tour starts immediately after the introductory presentation. All poster presenters are requested to be available at the posters in the poster area (1st floor) of the conference venue.

18:15 GET TOGETHER

KEYNOTE LECTURE

How to bring API production to Germany? - Engineering Aspects

Dr.-Ing. Michael Häberl, Merck Life Science KGaA, Darmstadt, Germany

Shortage or even absence of certain types of medicine in pharmacies and even hospitals have been in public discussion in Germany for quite a while and became reality for many patients. Certain antibiotics, medicine against breast cancer and fever are some of the most present examples. Only within the first six months in 2023 more than 100 new announcements of supply shortages were registered from the Federal Institute for Drugs and Medical Devices. Reasons are various and range from difficulties in the global supply chains to manufacturing problems and price limits especially for generic drugs.

While European manufacturers focus their investments on development and production of large molecules and biologics, the overwhelming part of small molecule APIs and starting materials is produced outside Europe, mainly in China and India. Too high investment and manufacturing cost and lengthy and complex permitting processes are disadvantageous for German production sites. Fluctuations in demands and the necessity to decide on investments for dedicated equipment, long before market introduction, cause significant risks of high idle cost.

To improve the competitiveness of our sites, we need to rethink our traditional production concepts. Backward integration, instead of focusing on the final production stages can make supply chains more resilient. Automated and flexible production equipment and a high level of asset utilization is needed for competitive manufacturing cost.

SESSION I:
API Synthesis

New approaches for targeting the intracellular allosteric binding site of GPCRs

Matthias Schiedel, Institute of Medicinal and Pharmaceutical Chemistry, Technische Universität Braunschweig, Beethovenstraße 55, 38106 Braunschweig, Germany

Recently, a highly conserved intracellular allosteric binding site (IABS was identified for several G protein-coupled receptors (GPCRs, including the chemokine receptors CCR2 and CCR9 [1-2]. Vercirnon, an intracellular CCR9 antagonist, even progressed to phase III clinical trials for the treatment of Crohn's disease, however, ultimately failed due to limited therapeutic efficacy [3], thereby exemplifying the high therapeutic potential but also the current limitations of intracellular GPCR antagonists. Thus, new approaches to improve the therapeutic efficacy of intracellular GPCR antagonism are urgently needed.

To discover new intracellular GPCR antagonists with improved therapeutic efficacy, we are following two distinct approaches that are both based on multifunctional ligands. On the one hand, we are developing fluorescently labelled ligands as molecular tools to study ligand binding to the IABS of GPCRs in a direct and straightforward manner. With the CCR9-targeted MHS-37 [4, 6] and the CCR2-targeted LT99 [5, 6], we developed the first small molecule-based fluorescent probes targeting the IABS of GPCRs. These tools showed a broad applicability and were used for cell-free and cell-based NanoBRET binding assays, fluorescence microscopy, and fragment-based screening approaches [4-6]. By applying MHS-37 as a screening tool, we discovered the 4-aminopyrimidines as a new class of intracellular CCR9 antagonist with improved affinity and antagonistic activity, compared to vercirnon. On the other hand, we are using the IABS of GPCRs as a drug target site for heterobifunctional proteolysis targeting chimeras (PROTACs to induce the proteasomal degradation of the respective receptor. With the CCR9-targeted MHS-33, we developed the first PROTAC addressing the IABS of GPCRs. In a proof-of-principle study, we showed that MHS-33 is indeed able to reduce CCR9 receptor levels, thus offering an unprecedented approach to modulate GPCR signal transduction [4, 6].

Literature: [1] Zheng, Y., et al., *Nature*, **2016**, 540, 458-461. [2] Oswald, C. et al., *Nature*, **2016**, 540, 462-465. [3] Wendt, E., et al., *Clin. Exp. Gastroenterol.*, **2015**, 8, 119-130. [4] Huber, M.E., et al., *Angew. Chem. Int. Ed.,* **2022**, 61, e202116782. [5] Toy, L., et al., *ACS Chem. Biol.*, **2022**, 17, 2142–2152. [6] Huber, M.E., et al., *Chem. Eur. J.*, **2023**, 29, e202202565.

Heading to phase I – Scale up of the production process of the antibiotic candidate Corallopyronin A into industrial scale

Miriam Große[b,h], Birthe Sandargo[b,h], Rolf Jansen[b,h], Tim Becker[c], Anna Krome[c], Andrea Schiefer[a,g], Silke Alt[f], Rolf Müller[e], Thomas Hesterkamp[f], Kenneth Pfarr[a,g], Karl Wagner[c,g], Marc Stadler[b,h], Achim Hoerauf[a,g]

[a] Institute for Medical Microbiology, Immunology and Parasitology, University Hospital Bonn; [b] Department Microbial Drugs, Helmholtz Centre for Infection Research, Braunschweig; [c] Department of Pharmaceutical Technology and Biopharmaceutics, University of Bonn; [d] Institute for Pharmaceutical Biology, University of Bonn: [e] Department Microbial Natural Products, Helmholtz Institute for Pharmaceutical Research Saarland; [f] Translational Project Management Office (TPMO), German Center for Infection Research; [g] German Center for Infection Research (DZIF), Partner Site Bonn-Cologne; [h] German Center for Infection Research (DZIF), Partner Site Hannover-Braunschweig

The natural product Corallopyronin A originating from *Corallococcus coralloides* inhibits bacterial DNA-dependent RNA polymerase [1]. It is currently developed to threat filariosis as primary indications and multiresistant *Staphylococcus* infections as secondary indication. To overcome process inhomogenities the product is produced with the recombinant producer strain *Myxococcus xanthus* [2]. Within the last six years, in the Helmholtz center for infection research (HZI) developed a robust bioprocess was developed, optimized and scaled up to technical scale. In average 80 mg/L CorA were produced batchwise and purified with an average yield of 60 %. Since 2016 the HZI provided more than 500 g of high quality research grade material (HQ-RGM; >90% purity) for formulation development, stability studies and preclinical trials.

In 2021, the Belgium Company Bio Base Europe Pilot Plant (BBEPP, Ghent, Belgium) was contracted for a feasibility study and further scale up of the drug substance production. The process was successfully implemented and scaled up to 15.000 L in March 2022. In average product titers of 77 mg/L CorA in the culture supernatant were produced. DSP was scaled up so that an overall yield of almost 40 % were achieved. Therefore, this is the first bioprocess with a recombinant myxobacterium that was performed in industrial scale. Currently the final chromatographic purification step is performed at the HZI the ensure product quality for final non-GMP preclinical tests including toxicity studies. In 2023 a company shall be contracted for (pre-)GMP production. The CMO would have the capacity to perform the complete USP and DSP process to deliver drug substance for formulation. The final drug product shall be used in trails for clinical phase I. Corallopyronin A might become the first antibiotic candidate that was brought to clinics by German academia without industrial support.

Literature:

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Mycelial pellets - an intertwined matter: How salt-enhanced cultivation affects product formation and filamentous cellular morphology

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One of the most promising new drug candidates for the treatment of various diseases are lantibiotics, which are ribosomally synthesized and post-translationally modified peptides produced by Gram-positive bacteria. The potency of lantibiotics against multi-drug resistant strains originates from their unique structure with unusual amino acids. An interesting subgroup of lantibiotics are the labyrinthopeptins, which have very attractive bioactive properties. Labyrinthopeptin A1 is a promising therapeutic agent, as it shows broad-spectrum activity against human immunodeficiency virus (HIV) and herpes simplex virus (HSV).

The filamentous bacterium *Actinomadura namibiensis* is the only known natural producer of this active pharmaceutical ingredient. Higher product yields are achieved under high osmolality conditions in submerged cultures, a procedure called salt-enhanced cultivation (SEC) [1]. In this case, the microorganism grows as nearly spherical hyphae agglomerates called *pellets*. Since product formation is directly linked to substrate supply to the biomass, methods for investigating inner and outer pellet structure, especially in regard to diffusivity and porosity, are crucial for efficient process development. Oxygen profiling measurements (carried out by a micro electrode penetrating the pellet step-wise) allow the investigation of oxygen supply inside pellets [2]. Moreover, the determination of diffusion coefficients using a second reference micro electrode has also been made possible. Thus, the micro electrode technique was coupled with inner and outer pellet structure investigations. The generated results showed that SEC has a significant impact on the morphological structure and oxygen supply of *A. namibiensis* pellets. At the same time, the influence of SEC on product formation of labyrinthopeptin A1 can be further clarified.

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Manufacturing through plant cell culture technology – sustainable, controlled and flexible in scale

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For more than three decades Phyton Biotech has been developing sustainable plant cell fermentation processes from a variety of plant species. Potential products for plant cell culture approaches range from active pharmaceutical ingredients to traditional herbal medicines, and ingredients for cosmetics and nutraceuticals.

The cultivation and production processes are executed in a controlled technical environment, independent from nature, resulting in high quality (GMP commercial grade active compounds.

In fact, for more than twenty years Phyton has used plant cell cultures successfully for the commercial production of paclitaxel (brand name “Taxol” – an active pharmaceutical ingredient (API broadly used in cancer therapies by pharmaceutical companies all over the world. Paclitaxel is derived from a class of Taxus species, specifically, the Yew tree.

The development of such a commercial plant cell culture-based process consists of several critical steps including the selection of high-producing cell lines, optimization of growth and production conditions, and establishment of a robust and reliable production process at the appropriate scale. A plant cell culture derived from a needle, leaf, or other tissue, combined with the development of favorable growth and production conditions, can result in a biotechnological manufacturing process that is sustainable, environmentally responsible, and cost effective.

Here, we will share our success story for producing paclitaxel – the most prominent plant cell culture-based process applied at an impressive 75,000 L scale.

SESSION II:
Scale-Up / Scale-Down Processes

Towards sustainable continuous production of crystalline APIs

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Despite the rising trend towards continuous manufacturing of active pharmaceutical ingredients (APIs), downstream processing is still a bottleneck. Although crystallization is an important purification step, as it is used in about 90% of all API production, it is usually performed as a batch process. A continuous crystallization and a continuously crystal process chain (CPC, see Figure 1), respectively, offering various advantages compared to the established batch processes, but come along with many challenges. Consistent desired critical quality attributes (QCAs), which are mostly the mean particle size, size distribution, polymorphic identity, and purity, can be reached due to steady-state operation. However, the downscaling of equipment is challenging, as production rates of 250 -1000 kg API per year only require flow rates of 10-100 mL/min. Moreover, due to high surface-to-volume ratios, encrustations are likely to occur and thus clogging issues arise.

In this contribution I present different kind of continuous crystallizer concepts to address these challenges. To complete the CPC, an apparatus for small-scale solid/liquid separation, washing and drying was developed and patented. The so-called modular continuous vacuum screw filter (CVSF) enables, through the clever connection to a continuous crystallizer, an end-to-end primary manufacturing process.

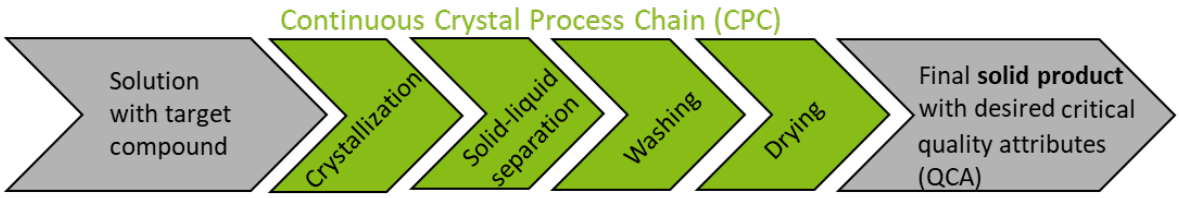

Figure 1 The path from crystal generation through crystallization to the solid end product with the desired critical quality characteristics via the crystal process chain

Scaling Up Crystallization Conditions for Achieving Targeted Crystal Morphologies of an Active Pharmaceutical Ingredient

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The morphology of crystals plays a crucial role in the processability and physicochemical behavior of active pharmaceutical ingredients (APIs. Different crystal shapes can impact the flowability, compressibility, dissolution profiles, and therapeutic efficacy of APIs. To achieve desired crystal morphologies, factors such as temperature, supersaturation, and solvent choice need to be carefully controlled. Experimental screenings on a small scale are commonly conducted to explore process conditions and identify optimal parameters for targeted crystal morphologies. However, it is important to acknowledge that directly scaling up from small-scale experiments to larger production volumes is not always successful, especially when there are significant differences between the small-scale setup and conventional stirred crystallizers used in industrial processes. Therefore, careful consideration and adjustments are necessary when transitioning from small-scale to large-scale production to ensure consistent outcomes.

In a previous study, advanced commercial miniaturized crystallization stirred systems were utilized to investigate and manipulate the crystal morphology of APIs. Specific process conditions were identified that consistently produced desired morphologies. However, there is currently a lack of experimental data to validate the transferability of these results to larger crystallizers. Thus, the aim of this study is to address this gap and investigate the scalability and applicability of the obtained crystal morphologies in a larger production setting. The upscaling process involves testing in a liter-scale crystallizer, representing a 200-fold increase in scale compared to the miniaturized device. By replicating the exact process conditions, including supersaturation profile, temperature, and solvent, from the small-scale experiments, the goal is to achieve comparable crystal morphologies. Success in replicating the morphologies on a larger scale would demonstrate the robustness and reliability of the identified process conditions, bringing us closer to achieving desired crystal morphologies for APIs in industrial-scale production.

Comparability of tablet compression characterization in small- and full-scale production

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Purpose

The United States Pharmacopeia (USP, Chapter 1062) gives methodologies for tablet compression in order to decrease tablet defects during production. However, it is rather difficult to achieve valuable trial results combined with little product loss. That is why small-scale systems have a high significance. The aim of this study was to identify if the results received in small-scale-tests are comparable to full-scale processes.

Methods

For small-scale, the “FLab10” from Fette Compacting GmbH (FC by Gamlen) was used (6mm flat-faced, n=3, 10 forces). Hardness, diameter and height were defined with a Tablet Tensile Analyzer (FC by Gamlen) and Mitutoyo Absolute (Mitutoyo), respectively. In full-scale, different settings on two rotary presses were used (FE35, 8mm convex (FC); F10i, 10mm flat-faced-facet, (FC), each with n=5, 5 forces, 2 turret speeds). Hight, diameter and hardness were analyzed with the MultiTest 50 (Sotax). Compactibility and compressibility curves of the used placebo blend (Lomapharm GmbH) were calculated acc. to USP using tensile strength calculation acc. to Pitt *et al*.[1].

Results

Overall, compactibility and compressibility curves were very similar for small-scale and full-scale. Only for compactibility, a less distinct increase of tensile strength at high compression forces was observed for convex tablets in comparison to flat-faced and flat-faced-facet tablets. This indicated that the tablet shape influences the hardness of the tablet by affecting the force distribution inside of the tablet, whereas differences between the machines and parameter settings have less impact for this powder blend.

Conclusion

It was successfully proven, that small-scale powder compaction analysis systems used to evaluate compression characteristics of formulations lead to comparable results obtained with full-scale presses. The parameter setup only had a minor impact on the results. Further trials are needed to investigate the impact of punch shapes.

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Multiscale morphology engineering for rebeccamycin production with the filamentous actinomycete *Lentzea aerocolonigenes*

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Microbial antibiotics are often produced by filamentous microorganisms such as the actinomycete *Lentzea aerocolonigenes*. In comparison to other prokaryotic systems handling filamentous species is rather challenging due to their complex cellular morphology ranging from dispersed mycelium to individual pellets. Thus, various *morphology engineering* strategies have been successfully developed in the past for tailor-made morphology alteration and thus for increased product formation.

Several morphology engineering approaches were applied to proof their suitability for *L. aerocolonigenes* cultivations in regard to their effect on cellular morphology and rebeccamycin product synthesis. In this context, the individual or joined supplementation of glass particles of varying sizes (inter alia, x_{50} = 969 and 7.9 µm) as well as the emulsifier soy lecithin lead to an up to 15-fold average increase in product formation in shaking flask cultivations. Hereby, light was shed on the mechanistic interaction of the supplements with the filamentous pellets and the subsequent structural changes [1,2].

As the challenging morphological behavior of *L. aerocolonigenes* averts a scale up into a conventional stirred tank reactor (STR), a membrane gassing unit (MGU) (**Fig.**) was developed and successfully implemented into parallelized 3 L lab-scale STRs.

Additional morphology engineering strategies already established in shaking flasks for *L. aerocolonigenes* enabled a significant overall rebeccamycin production in the novel MGU-STR system with minor destruction of biomass due to excessive mechanical shear gradients originating from bubble formation, rise and especially bubble decay.

Figure: Membrane gassing unit (MGU) for bubble-free gassing in stirred tank bioreactor.

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A Robotic- and AI-Assisted Accelerated Tablet Formulation and Process Design Platform

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Traditional methods of developing drug products for a new active pharmaceutical ingredient are time-consuming, costly and often inflexible. The selection of the right excipients in tablets and process conditions are crucially important as they can impact manufacturability, performance and stability of the drug product. Formulation optimisation studies are conducted to identify a robust formulation that can meet manufacturability criteria (e.g. flowability, tensile strength while fulfilling the desired performance targets, e.g. release of > 80% of the drug in less than 30 min. This is a multidimensional problem with a high degree of interdependence between raw material attributes, process parameters, and drug product properties. This talk will present a high-throughput, data-intensive micro-scale tablet development system that can automatically prepare and measure powder, and produce and test single tablets. By employing robots, the system combines an automated dosing unit, a dedicated powder transportation unit, near-infrared spectroscopy for evaluating powder blend homogeneity, a compaction simulator, and an automated testing system for measuring tablet properties. The data is automatically structured and fed into a data fabric for the development of a hybrid system of models, including mechanistic and data-driven approaches, to predict critical powder blend (e.g. flowability and tablet attributes (tensile strength, porosity from raw material properties. This talk will further discuss the combination of hybrid modelling approaches with model-based optimisation and the micro-scale tablet development system. This approach significantly reduces hands-on-lab time (> 80%, material, and waste, offering significant potential for accelerated and sustainable drug product development.

KEYNOTE LECTURE

Pharmaceutical Engineering at Nanoscale: Delivery of RNA and more"

Heinrich Haas, Johannes-Gutenberg-Universität, Mainz, Germany

The successful development of messenger RNA (mRNA) for vaccination against Covid-19 has highlighted the potential of mRNA for application not only in vaccines, but also for a variety of therapeutic applications including, but not limited to, tumor (immuno)therapy, protein substitution or gene therapy. mRNA as a very large, highly charged, and labile biopolymer re uires delivery systems to allow pharmaceutical application. As delivery systems, currently LNPs, which are manufactured by a specific protocol with a defined mixture of four lipids are in the center of attention. Further to that, there are several other nanoparticle formats which have demonstrated to be promising as delivery systems for RNA and other drugs.

Here some concepts for nanoparticle engineering based on lipids and polymers are presented, which allow for tailoring of the delivers system according to type of (RNA) cargo, application route and the intended therapeutic intervention.

SESSION III:
Solid Dosage Forms

Material Characterization in Drug Product Development of Oral Solid Dosage Forms – an Industry Perspective

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Lena Mareczek, Merck Healthcare KGaA, Darmstadt, Germany; Meike Harms, Merck Healthcare KGaA, Darmstadt; Stephan Reichl, Technische Universität Braunschweig, Braunschweig, Germany

The knowledge of material properties which are crucial for manufacturability as well as for the critical quality attributes of the final drug product is a very important aspect of drug product development as well as its quality by design principles. Material characterization is a multidisciplinary endeavor involved beginning from drug substance particle engineering to in process control of the final tablets.

Processability prediction in drug product manufacturing

In drug product development, material properties need to be described by appropriate analytical methods for both the active pharmaceutical ingredients and the excipients. Ideally, standardized methods are available which can be ranked against a specified processability target. As such, the data can be used for formulation and process selection as well as optimization of the drug substance to create an utmost robust product. By applying statistical analyses like multivariate data analysis or utilizing previously built prediction models for the different unit operations, the processability of the different intermediates during the drug product manufacturing process can be estimated.

Troubleshooting by material characterization

Not only standardized methodologies but also dedicated method development for issues along the process chain is an important aspect in the field of material characterization. Depending on the unit operation, those issues can be related to flowability, fluidization, chipping, pneumatic conveying or insufficient hardness to name a few. A selection of real-world use cases is presented.

Loading of oily ink formulations on structured orodispersible film templates for patient individual drug dosing

Lena Mahlberg, University of Tuebingen, Department of Pharmaceutical Technology, Germany, Denise Steiner, University of Tuebingen, Department of Pharmaceutical Technology, Germany

For the treatment of special patient groups with issues in swallowability like children or the elderly, orodispersible films are a suitable delivery platform due to their fast disintegration in the oral cavity. In combination with a 2D printing process of drug-containing inks on plain templates, they can additionally be used for patient individual drug dosing [1].

To minimize smearing effects during the loading process, structured orodispersible film templates (SOFTs) were used in this study [2]. Due to an increasing number of poorly water soluble drugs classified in BCS class 2, Griseofulvin was chosen as a model drug, which also has a low solubility in lipids, such as medium-chain triglycerides (MCT). It was formulated in a lipid-based, water-free nanosuspension which could be loaded onto the SOFTs without causing a disintegration of the hydrophilic film structure.

For ink preparation, Griseofulvin was wet milled directly in the liquid lipid MCT using a dual centrifuge equipped with grinding beads. Stabilization of the particles was occurred with Phospholipids (Lipoid S20). During film loading, a defined ink volume was printed onto the SOFTs. The particle sizes of the Griseofulvin suspensions were measured during dual centrifugation and after film-loading by disintegrating the films. Furthermore, the SOFTs were characterized according to their mechanical properties and the dissolution behaviour of Griseofulvin from the films was investigated.

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SESSION IV:
Semi-Solid & Liquid Dosage Forms

Current trends in dermal and transdermal drug delivery

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Dermal and transdermal drug delivery has several advantages over conventional routes of administration. In the case of dermal administration, these are mainly the high drug concentration at the site of application and the minimization of side effects, whereas the systemic transdermal administration offers continuous drug delivery over a long period and circumventing the first-pass effect. For both, however, the main obstacle is the impermeable barrier located in the upper skin layer, the *stratum corneum*. This layer is the final product of keratinization of the epidermis and consists of corneocytes surrounded by a lipid matrix containing mainly ceramides.

The excellent skin barrier and limiting physicochemical properties of drugs (poor solubility and permeability are the main reasons for the low bioavailability from conventional dosage forms such as ointments, creams or gels. Therefore, considerable efforts have been made to develop specific skin delivery technologies which can be divided into three main groups, namely the *chemical* (e.g., permeation enhancers or *physical* (e.g., iontophoresis, electrophoresis, microneedles enhancement approaches, and application of *colloidal drug nanocarriers* (e.g., vesicular systems, polymer or lipid nanoparticles.

Quantum dots nanoemulsion as a fluorescent tool for labeling zebrafish cells to study neurodegenerative diseases

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Introduction: Nanofluorescent probes, specifically quantum dots, can overcome obstacles in brain imaging due to their small size and resistance to photobleaching. Combined with specific biomolecules, they can improve neuronal cell uptake for more effective cell type-specific imaging[1,2]. Herein, we investigate the advantages of encapsulating QDs into nanoemulsions and evaluating their effects as a fluorescent drug delivery system helpful in treating neurodegenerative diseases using zebrafish as an *in vivo* model. **Methodology:** We injected free and nano-emulsified QDs into 3-5dpf zebrafish larvae to study internalization at varying concentrations. We also looked at toxicity and cell labeling using transgenic zebrafish models. **Results and Discussion:** CdTe-Qds (red emission) displayed no toxicity below 0.5 mg mL-1, while carbon dots (blue emission) did not reveal signs of toxicity over a range of < 4.0 mg mL^{-1}. Vascular injections demonstrated that carbon and CdTe QDs were quickly distributed in the zebrafish vasculature and eventually accumulated in the lymphatic system. Nanoemulsions allowed a more sustained release and longer retention of QDs inside the circulatory system. Upon brain ventricle injection, significant fluorescence was detected in the extracellular space of neuronal tissue; over time, a potential buildup in lymphatic brain cells could be noticed. **Conclusions:** QDs display different levels of *in vivo* toxicity depending on their composition. Nanoemulsions can improve drug distribution, while the fluorescence properties of QDs can be exploited as a contrast agent to facilitate imaging studies of administered compounds in the central nervous system.

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Keywords: quantum dots; zebrafish; fluorescent probes; neurodegenerative diseases

Controlled release from lipid nanoparticles by modification of drug lipophilicity

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Due to their physiological components and structure, lipid nanoparticles (LNP) are an interesting carrier system for targeted drug delivery. In order to take advantage of potential benefits, such as favored phagocytosis by macrophages, it is necessary to ensure that the incorporated drug remains associated to the particles until they reach the site of action. Knowledge of the drug release behavior is therefore essential.

Since the release of a drug from the droplets of a lipid nanoemulsion depends on its lipophilicity, prodrugs of increasing lipophilicity were designed. Their transfer behavior from LNP into lipophilic acceptors, as well as that of other lipophilic model drugs, was investigated in porcine serum and (model) blood via differential scanning calorimetry (DSC) [1]. The transfer rates ranged from burst to prolonged and potentially degradation-controlled release. Furthermore, the retention times of the model (pro-) drugs on a C18 reversed-phase HPLC-column were studied under isocratic conditions [2], enabling the rapid estimation of a drug's release behavior from liquid LNP. The combination of drug release and HPLC data may provide useful guidance for the synthesis of lipophilic prodrugs in order to exploit LNP for drug targeting strategies.

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SESSION V:
Digital Models in Pharmaceutical Manufacturing

Process analytical technologies for inline control of fluidized bed agglomeration using artificial intelligence

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The industrial-scale production of innovative products requires state-of-the-art technologies. Fluidized bed processes offer almost unlimited possibilities in terms of optimized particle design and the functionalization of products. Using fluidized bed agglomeration technology, product stability and functionality as well as subsequent processability can be significantly improved. To ensure optimal processes and reproducible product properties fluidized bed plants have to have powerful integrated control strategies.

Material and method

Artificial neural networks are a powerful tool to correlate input data (e.g., material properties, quantities, temperatures, pressures with output data (e.g. bulk density, composition, homogeneity, morphology, particle size, humidity. Any fluidized bed process can be characterized by process conditions of granulation itself and material properties of raw materials and final granules. By changing processing parameters for given technical configurations of fluidized bed systems, final properties of granules as well as their behavior in later application can be adjusted properly. Innovative process analytical tools must be integrated into the granulation system and their output can be used for product property-based control of the granulation conditions.

It is generally strongly recommended to study agglomeration in detail in lab-scale before industrial usage. A study based on Design of Experiments (DoE has been carried out to get better understanding of parameter-property-relations and to evaluate optimal control strategies regarding sensitivity and robustness. All relevant process and product data were electronically recorded and processed using an artificial neural network to derive a validated process model.

Results and discussion

In the presented case study, DoE and process modelling were applied for detailed evaluation of the spray agglomeration process as well as the influence of resulting product properties on the tabletability. Finally, a process model based on artificial neural networks (aNN could be developed. Based on its prediction an automatic control of particle growth kinetics has been successfully derived.

In-silico supported methods (COSMO-RS for the sustainable and targeted extraction and isolation of natural products from side-streams of wine production

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The wine production generates tremendous amounts of organic waste. These side-streams still contain largest amounts of extractable antioxidative, cardioprotective and antiproliferative natural products, such as the famous stilbenoid *trans*-resveratrol [1]. It's use in dietary supplements, as well as in cosmetic products, create a strong scientific and economic interest in novel solvent-free or ecologically safe extraction and isolation methods.
In-silico methods can be used to pre-evaluate potential solvent systems for the extraction and isolation of natural products from side-streams and guide to a sustainable laboratory operation. These methods include the "***Co**nductor like **S**creening **Mo**del for **R**eal **S**olvents*" (COSMO-RS, which can be used for calculation of compound specific chemical potentials and their solubility to be estimated from them [2,3].
Environmental friendly alternatives for solvent-free extraction of natural products are "***N**atural **D**eep **E**utectic **S**olvents*" (NADES which were first described in 2011 [4]. NADES are mixtures of organic solids which, after appropriate processing, already turn into a transparent liquid at ambient temperature. They consist of a combination of *hydrogen bond donors* (HBD and *hydrogen bond acceptors* (HBA, and provide polarity ranges comparable to those of organic solvents.
In order to consider a variety of possible combinations of HBA (e.g. betaine, choline chloride and HBD (e.g. malic acid, glucose for targeted extraction of resveratrol, *COSMO-RS* was applied as *in-silico* method. After the selection of suitable combinations of HBA and HBD, an ultrasonic-assisted extraction of the grapevine material was performed. Results of resveratrol contents in NADES extracts were determined by UHPLC-DAD analysis.
Countercurrent chromatography (CCC isolation of pure resveratrol from the commercial grapevine extract (Vineatrol®30 was used as effective application. To reduce the time-consuming search for a promising two-phase solvent system, *COSMO-RS* was tested to calculate the phase composition and solutes partition coefficients. As a result, the grapevine extract was pre-separated by *high-performance countercurrent chromatography* (HPCCC, semi-prep. coil column: 125 mL, Dynamic Extractions, U.K. in *head-to-tail* mode (separation A: n-hexane/ ethyl acetate/ methanol/ water 'HEMWat' (1/2/1/2; *v/v/v/v*. Phase compositions and solutes partition coefficients for separation B were calculated. Based on these optimized *separation factor α* and K_D values, the solvent system HEMWat (1/1.5/1/1.5; *v/v/v/v*) was carried out to separate the resveratrol containing *heart-cut* fraction in *head-to-tail* mode.
In-silico supported ultrasonic-assisted NADES-extraction was successfully applied for the targeted extraction of resveratrol from side-streams of wine production. *COSMO-RS* was used in combination with *countercurrent chromatography* to find a useful two-phase solvent system for preparative isolation of resveratrol. *In-silico* calculations on NADES extraction combined with CCC solvent system prediction are powerful combination to sustainably extract, recover and isolate natural products with potential scientific and industrial interest.

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Development of a method for AI supported crystallization process control

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Crystallization is an important step in many pharmaceutical processes. It is used for purification and separation of many different APIs. The properties of these crystals not only have a significant impact on the bioavailability and shelf-life of the produced drug, they also have an effect on the efficacy of unit operations further downstream during production [1]. Because crystallizations are very complex, in most cases the process control has been static and based on empirical trial-and-error optimization, since no models to link process parameters to crystal quality are available. Only with the advent of *Process Analytical Technology* (PAT in the last decades and more research on the mechanisms of crystallization, more sophisticated and dynamic process control approaches have been suggested [2].

Generally, process control strategies for crystallizations can be divided in to categories: Model-free approaches usually feature pre-defined profiles for process variables like temperature or oversaturation. Other model-free approaches are methods like *Dynamic Nucleation Control* (DNC which dynamically change process parameters based on the difference between a pre-defined ideal trajectory of a process variable (e.g. particle size and its online PAT-measurements [3].

For a more fine-grained process control, model-based solutions have been developed. A prominent example is the *Model Predictive Control* (MPC using a mathematical model to predict the future development of process variables online. Predictions and a pre-defined ideal trajectory of a target parameter are then used online by an optimizing algorithm to determine optimal control outputs for the process. One drawback of model-based process control is the model itself. Since crystallizations are very complex, designing a suitable model accounting for all relevant effects like impurities, agglomeration and crystal breakage is a difficult and time-consuming process [4].

With computing power getting cheaper in the last decades, the employment of machine learning is becoming a more and more viable way to combine the advantages of both model-based and model-free process control by (partially replacing hand-crafted mathematical models with data driven ones.

At the Institute for Chemical and Thermal Process Engineering (ICTV) of the TU Braunschweig, a method for process control of crystallizations using an *Artificial Neural Networs* (ANN) is being researched. The ANN is used to predict relevant process variables in its place and used in a modified MPC, replacing the fully mechanistic model that is usually used for this purpose. Since it is difficult to train one single ANN that can make valid predictions for many different crystallization processes with varying parameters and substances, the focus here is to develop a method for quickly training ANNs for specific use cases.

The developed method includes the aggregation of existing or the generation of new process data, which is then preprocessed and used for training the ANN. Training parameters and ANN configuration can be modified for the specific crystallization task at hand. For good visibility and reproducibility, the training itself is tracked. If an ANN shows good prediction accuracy, it can then be integrated into an MPC for optimal control.

A first version of the method is presented, with which an ANN was trained and used in a modified MPC for controlling a batch cooling crystallization process in a lab-scale stirred reactor.

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Learning Adsorption Processes with Physics-Informed Neural Networks: A Parameter Sensitivity Perspective

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Physics-informed neural networks (PINNs) offer an interpretable predictive model by incorporating prior physical knowledge, a feature especially beneficial in digital models in pharmaceutical manufacturing where data can often be scarce or noisy (Cuomo et al., 2022). Once parameterized, PINNs can enable real-time control, optimization, and soft sensing, making them instrumental in predicting process parameters and hidden dynamics of critical quality attributes (Cuomo et al., 2022). Our work extends the study on PINN-based estimation and algebraic identification methods in pharmaceutical manufacturing (Selvarajan et al., 2022), identifying issues with measurement noise amplification and standard parameter sensitivity concepts' inadequacy (Abt et al., 2018). We present a customized design of experiment (DoE) strategy, specifically designed for investigating parameter sensitivities in PINN-based scenarios. Our case study used this framework in an adsorption process model, showing that traditional uncertainty quantification methods underestimate parameter uncertainties. However, the proposed DoE strategy mitigates uncertainties in the examined adsorption model and promises enhanced reliability for PINN-based parameter estimates in various manufacturing scenarios in general.

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Perspectives of Work in Pharmaceutical Production

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The traditional pharmaceutical production system is outdated, as it can be classified as Industry 2.0 mature with 3σ quality level. To deliver pharmaceutical innovation to patients quicker and more reliably, production must advance to a higher level of maturity. The pharmaceutical production of the future will operate by automation, continuously and based on digital technologies, including generative AI. Staffing will be minimized and consists largely of scientists, data experts and process engineers. Its realization still requires major research efforts in natural sciences, data analytics and engineering.

SPECIAL GUEST

EU Funding & Policies for Research and Innovation: A Companion for a Research Career ?

Inga Benner
European Liaison Office of the German Research Organisations (KoWi)
Consultant for Cluster 1 (Health), EIC (Pathfinder)

An overview of opportunities in EU funding for SPhERe participants – from junior to senior researcher. From basic research, funding for transnational mobility to more traditional collaborative projects all the way to deep tech innovation: The presentation will pinpoint what types of activities could be worth applying for and how and why integrating EU funding in a longer term career plan might make sense for a researcher.

Rather than going into detail on how each programme works, the speaker will give impulses and illustrate with examples of call topic or sample projects.

Participants will also learn about the offer the European Liaison Office of the German Research Organisations (KoWi) and how they might benefit best from these on an individual or organisational basis.

SESSION VI:
Analytics, PAT

Benefits of using UV-Vis, NIR and Raman spectrometers as inline PAT in pharmaceutical application

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Dr. Andreas Berghaus, ColVisTec AG, Berlin, Germany

The pharmaceutical industry is seeking efficient technologies to monitor and optimize product development and production processes while ensuring product quality and safety. As a versatile analytical tool, spectroscopy (UV-Vis, NIR, and Raman offers enormous potential for inline process analysis in the pharmaceutical industry.

Spectroscopy enables quantification of critical quality attributes, such as chemical composition, structural conformation, and impurity identification. In addition, spectroscopy enables the monitoring of important process parameters such as reaction kinetics, crystallization, and drying processes.
Multivariate data analysis techniques enable real-time process control and optimization. Spectroscopic data can be transformed into actionable insights through the use of chemometric models and statistical analysis. These insights support process monitoring, endpoint determination, real-time release testing, and quality assurance, facilitating the implementation of process analytical technologies (PAT and supporting quality by design (QbD principles.

Pharmaceutical development and pharmaceutical manufacturing differ in terms of innovation drivers and barriers, cost benefits, quality benefits, and time-to-market advantages. Regulatory hurdles to introducing a new or even additional technology such as inline spectroscopy into an established manufacturing process are significant and may prevent its adoption. The development phase of a pharmaceutical product is less constrained and at the same time has the advantage that any technique that enables a shorter time to market represents a cost saving with a very large advantage, taking into account intellectual property.

Inline spectroscopy is an approach that enables faster process development and offers significant advantages in terms of time savings and cost reduction over traditional offline analytical methods.

Online coupling of size exclusion chromatography to Raman spectroscopy for protein analysis

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Biopharmaceuticals, i.e. therapeutic proteins, are a steadily growing business area of the pharmaceutical industry. The therapeutic effect of a protein is determined by its highly specific secondary and tertiary structure. Any changes in this structure can lead to a loss of their pharmaceutical activity. Thus, therapeutic proteins have a significantly higher complexity than low-molecular weight (small active pharmaceutical ingredients (API and are more susceptible to environmental influences. Therefore, fast analytical techniques that allow for a direct verification of structural integrity are of major interest.

Raman spectroscopy (RS is a powerful technique for structural analysis of proteins and other compounds. In combination with size exclusion chromatography (SEC, proteins can be separated from matrix components without compromising their native structure. Thus, online coupling of SEC and capillary-enhanced RS (CERS enables structural assessment and identification of proteins in biological samples or biopharmaceutical formulations. Chromatographically separated proteins are excited coaxially while flowing through the pathway of a liquid core waveguide (LCW. The Raman scattered light is then detected in backscattering geometry. The online coupling of SEC and CERS was successfully applied for the identification of different proteins such as rituximab or bovine serum albumin in matrix samples, i.e., biopharmaceutical formulations and biological fluids. SEC enables a straightforward separation of the proteins form the matrix components, e.g., formulation excipients. Consequently, Raman spectra of protein therapeutics can be obtained that provide information of protein structure from the original formulation without any extraction steps.

A-TEEM spectroscopy for fast and efficient QC and PAT of liquid samples

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HORIBA is on the way to establish A-TEEM technology as a new standard for analysis of liquid samples in biotech and pharma applications. The usability ranges from R&D to QC and PAT. We want to give a short introduction about A-TEEM, its benefits, application examples and about the Aqualog absorbance and fluorescence spectrometer that allows fast measurements and high sensitivity at low operating costs.

In-situ Characterization of Cells in a Bioreactor by Ultrasound enhanced in-line Raman and ATR-FTIR Spectroscopy

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Acoustic radiation forces are exerted on particles in suspension when exposed to ultrasound. This effect can be exploited to locally enhance their concentration in an ultrasonic standing wave - in other words an in-line sample of the solid can be generated directly inside the process. This technique was applied on fermenting cells in a culture to assess insights of process parameter in-line by combining non-destructive analytical methods like Raman and infrared spectroscopy with an ultrasonic trap, e.g., with FTIR-ATR to detect the product inside the cells [1, 2].

The exact characterization of the physiological state of the cells during a fermentation enables a highly accurate process control. In this work we used a soniccatch (usePAT, Vienna) with aforementioned vibrational spectroscopy methods for monitoring the fermentation process and identifying optimisation potentials.

This was shown by the assessment of yeast cells with Raman spectroscopy in a classical bioprocess. The in-line acquired spectra of the yeast cells reveal the different chemical composition of the intracellular makeup during the fermentation. A more sophisticated approach was chosen when the selectivity of an FTIR ATR probe was tremendously improved by the application of soniccatch. Here, the combination of the two technologies was able to detect the PHB content of Cyanobacteria directly inside a bioreactor.

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SESSION VII:
Microsystems for Pharmaceutical Testing

Droplet-based microfluidic screening: from basics to precision oncology

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Microfluidic platforms offer the possibility to carry out screening tests effectively and inexpensively. This not only applies to the pharmaceutical testing of active substances, but also to biomedical research. The resource-saving design of the microsystems, the high flexibility in terms of inputs, local and temporal processing steps, and high-throughput concepts are increasingly making them an universal tool in biomedicine and pharmacy.

A microfluidic platform based on a droplet-based system has been developed at iba, using e.g. spheroids as models for tissue interactions. By alternating polar (cell medium and non-polar (Perfluorodecalin [PFD] liquid phases, many hundreds of drops in a tube reservoir can be manipulated and detected separately. Each droplet in the high-throughput process represents a microhabitat in the nanoliter range to cultivate three-dimensional cell cultures. The system is designed to control and manipulate spheroids by adding media and reagents. Surveillance by non-invasive optical and electrical sensors is automated.

The flexibility of the platform for biomedical-pharmaceutical research is shown using research examples from the areas of study of the development of spheroids in droplets, drug screening based on 3D cell structures and study of infection processes.

Development of an automated and fully sensor equipped capillary-wave microbioreactor for biopharmaceutical research

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Nowadays, new devices for fast screening and parallel testing of active pharmaceutical ingredients (APIs) are needed. Especially automated and highly parallelized microbioreactors (MBRs) with a volume in the lower microliter scale are able to close this gap. Their main advantage is the generation of a large amount of process data by integrated sensors in a small volume, which helps to save expensive media components and, at the beginning of drug development, to test the drug candidates that are still present in small quantities. Furthermore, the automation and parallelization minimize the number of work-intensive experiments.

Therefore, a new MBR with a volume of 7 µL was developed for application in biopharmaceutical research [1]. The MBR consists of a quadratic glass chip holding a sessile droplet of cultivation medium in a round cavity. The droplet is mixed by vertical oscillation inducing capillary waves on the droplets surface. Due to this technique, the MBR is called *capillary-wave microbioreactor* (cwMBR). k_La values above 340 h^{-1} and mixing times below 2 s can be achieved with this vertical oscillation [2]. For addition of liquids such as testing substances, an automated liquid handling system was integrated in the cwMBR platform. Furthermore, the processes can be characterized by inserted optical sensors for pH, oxygen and glucose. Additionally, absorbance and fluorescence can be measured for cell-based assays or detection of cell growth [3]. With the help of these sensors, a full characterization of biotechnological cultivations is possible. Moreover, the cwMBR can be applied for biopharmaceutical experiments including viability studies and phagograms.

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Real-time monitoring of cell confluence and barrier integrity of an endothelial monolayer on an ultrathin nanoporous membrane with a bioimpedance sensor.

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In organ-on-chip systems for *in vitro* modeling of barrier tissues, integrated electrical sensors and porous membranes are key elements. Here we present a complete biological microelectromechanical system (BioMEMS). It comprises a coplanar sensor for bioelectrical impedance spectroscopy (Bio-EIS) monolithically integrated on an ultrathin nanoporous membrane (pore size: 500 nm, membrane thickness: 700 nm) made of Si_xN_y. Compared to conventional PET membranes, this membrane is characterized by very high optical transparency. The microfluidic chip is connected to a home-built readout device using a 3D-printed holder. To test the concept, human umbilical vein endothelial cells (HUVECs) were cultured in the microfluidic chip at different concentrations for two weeks and subjected to bio-EIS measurements every 12 hours. The bio-EIS data were analyzed using equivalent circuit analysis based on Nyquist plots, which showed discernible cell behavior such as cell population growth, confluent monolayer formation, and tightened cell-cell contacts. Electrical measurements were verified by fluorescence staining. A subset of the Bio-EIS data was used to train a machine learning algorithm using 1-Dimentional-Convolutional neural network (Conv1d) to build predictive models for detecting distinct barrier growth phases. This allowed the prediction of four different barrier stages (from seeding to forming a dense endothelial barrier) with 97% accuracy. In the future, we will use this powerful tool to explore the influence of shear stress and various tight junction modulators (TJMs) on the integrity of the cell barrier.

API SYNTHESIS

Polymeric Ionic Liquids (PILs-based Hydrogels as Immobilization Material in Catalytic Reactors

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Hydrogels based on Polymeric Ionic Liquids (PILs) are a promising immobilization material for catalyst recovery due to their mechanical and chemical stability. To adjust their properties, such as swelling behavior, to their purpose, the composition can be modified. Thus, various PILs-based hydrogels can be synthesized through radical polymerization of an ionic liquid, such as 1-Vinyl-3-ethylimidazolium bromide (VEtImBr) or 1-Vinyl-3-*iso*propylimidazolium bromide (V*i*PrImBr), and a crosslinker, *N,N`*-Methylenebisacrylamide (MBAA) or Tri(ethylene glycol) divinyl ether (TEGDVE). These combinations were studied with regard to their application in catalytic reactors.

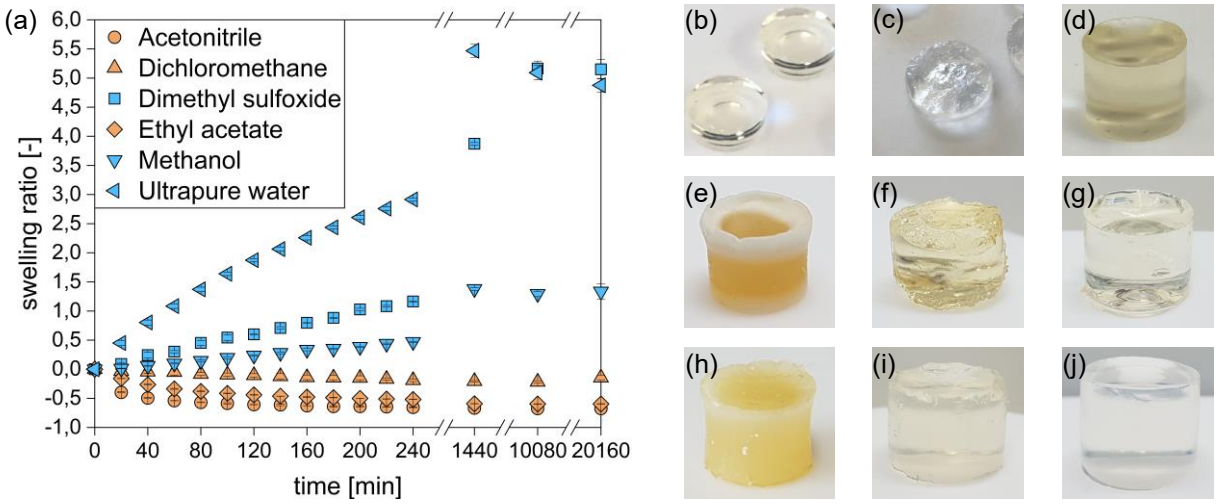

Figure 1: Abrasion and swelling behavior of poly(V*i*PrImBr/MBAA)-hydrogels at 23 °C (a) swelling behavior in 40 mL of different solvents; (b) fresh small cylindrical hydrogels; (c) hydrogel after 72 h at 350 rpm after 7 days in 0,9 % NaCl solution at 25 °C; (d) fresh large cylindrical hydrogel. Hydrogels after 24 h in (e) acetonitrile; (f) dichloromethane; (g) dimethyl sulfoxide; (h) ethyl acetate; (i) methanol and (j) ultrapure water.

Information on the swelling and shrinking of hydrogels are useful to reduce catalyst leaching by changing the composition of the reaction mixture. The swelling behavior depends strongly on the selected solvent (Figure 1). Besides, they affect the appearance of the hydrogel. While hydrogels shrink most in acetonitrile and show a firm texture, they swell most in ultrapure water and show a very soft texture. Another recent challenge is catalyst loss through abrasion caused by mechanical stress in reactors. This was studied in a reactor-like setup after equilibrium swelling. Attrition was found to increase with rotational speed and stress time, illustrated in Figure 1(b,c).

SCALE-UP / SCALE-DOWN PROCESSES

Developing a biocatalytic multiphase reaction scale-down model

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Microbioreactors (MBRs) are increasingly being viewed as very promising technology to facilitate acceleration of process development. Incorporating several advantages at the microscale (small volume, parallelization, online sensors and automation) offers time saving, cost reduction and quantitative data monitoring in real time during early stages of process research. There remain challenges – including mixing in laminar flow regimes or mass transfer – that continue to impede widespread adoption of this promising technology. The combination of emerging manufacturing techniques like additive manufacturing (3D-printing) and modeling with Computational Fluid Dynamics offers new possibilities for fast design changes in MBRs with rapid prototyping.

This study presents a fully modular micro bubble column reactor (MBCR) mostly made of 3D-printed parts. The reactor (700 µL) is completed with reusable glass slides carrying optical micro sensors for pH and oxygen measurements. The MBCR is mixed with a steady gas stream through a nozzle at the bottom and its biological applicability was shown with cultivations of model organism *Escherichia coli*[1].

The MBCR system is notably suitable for biocatalytic-based gas phase fermentation, since the gas stream is not limited to air or oxygen – but can be utilized to supply gaseous educts (e.g., butane)[2] and save significant amounts of these educts due to the small volume (up to 400-fold). Safety concerns can thus be drastically reduced when working near explosion limits, or even under explosive atmospheres. Utilization as a scale-down model allows for multiplication of experiments for process parameter investigation with pre-determined layouts by design-of-experiment procedure. Overall, application of the 3D-printed MBCR opens up new horizons for rapid, comprehensive and cost-effective studies of enzymatic multiphase reactions.

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Development and Scale-up of a Modified Release Bilayer Tablet based on Compaction Simulation

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Introduction and Aim

Drug delivery systems with modified drug release have become an increasingly important branch of drug research in recent years due to their numerous advantages. In this context, preparations a single daily administration can increase patient adherence and reduce side effects. Multilayer tablets as dosage form can offer different release profiles while combining different active pharmaceutical ingredients (API) in just one tablet. The aim of the present work was to develop a bilayer tablet with immediate and prolonged release of the API Diclofenac based on compaction simulation and subsequent transfer to a production rotary press.

Methods

Formulation development of the bilayer tablet was supported by ZoomLab^{TM} digital formulation assistant, the tableting process parameter design frame was investigated on a compaction simulator (STYL'One Evolution) and the process was then transferred to a production rotary press (KORSCH X 3). Mechanical tablet properties and dissolution profile of the API were investigated target parameters.

Results

With the help of a digital formulation assistant and compaction simulation a material sparing and fast bilayer product development was successfully performed.

The mechanical tablet properties produced by compaction simulation and rotary press production did not differ significantly from each other so that compaction simulation predicted large scale production effectively. It could be shown by means of the similarity factor f2 that also the dissolution profiles of the tablets produced by compaction simulation and rotary press production were similar. The present results imply that the transferability of the production of bilayer tablets with modified drug release from the compaction simulator to a rotary press is given.

SOLID DOSAGE FORMS

Production of self-dispersible lipid pellets by jetcutting

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Polymedication leads to major adherence problems for many patients. Individualised dosage forms containing different active pharmaceutical ingredients (APIs) may be a solution here. Since a large proportion of the new APIs are poorly soluble in water, the aim of this work is to produce self-dispersible lipid pellets that can be used as carriers for such active ingredients. Due to their size in the upper micrometre range and their spherical shape, pellets are well suited for filling capsules, which could easily be used for patient-specific drug combinations.

A JetCutter Type S (geniaLab, Germany) is used to produce the pellets. In this device, the previously melted lipid is pumped through a nozzle, and a rotating wire tool then cuts the liquid jet into segments of equal size. The segments are formed into spherical droplets by surface tension during flight which are then solidified in liquid nitrogen. Droplet formation and flight, observed by stroboscopic light, are mainly influenced by lipid flow rate and motor speed of the cutting tool. The number of wires in the cutting tool also affects droplet formation and, therefore, pellet size and shape.

Pellets containing Gelucire® 48/16 as the lipid material have sizes between 700 and 1200 µm and a round shape with a sphericity of up to 0.93, depending on the process parameters. However, when the lipid is loaded with 3 wt. % fenofibrate, the API crystallises on the surface of the pellets This phenomenon is probably due to the extreme temperature difference when the droplets are solidified in liquid nitrogen, which is why the experimental set-up is going to be optimised for this type of pellet hardening.

Preparation of self-dispersible pellets by extrusion-spheronization

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Multimorbid patients, who suffer from several diseases at the same time, often depend on polymedication. Polymedication is defined as the use of five or more drugs per day. Especially in the elderly, polymedication can lead to medication mix-ups, confusion about the dose regimens and poor adherence to therapy.

Patient-individualized capsules are an interesting option to simplify and optimize the administration of multiple drugs by adjusting the content of the capsules according to the needs of the individual patient in terms of type and dosage of medication.

Pellets, spherical particles with a diameter of about 0.5 to 1.5 mm, may be used as filling for patient-individualized capsules.

In order to improve the dissolution properties of poorly water-soluble drugs, the water-soluble surfactant Gelucire® 48/16 (polyoxyethylene-32-stearate) was used in the current study to develop self-dispersible pellets as filling for patient-individualized capsules. The pellets were prepared by extrusion-spheronization. In a semi-continuous process, Gelucire® 48/16 was first formed into strands with a length of about 0.5 m using a twin-screw extruder. The strands were then cut into pieces of about 2.0 mm in length with a modified strand cutter, and were finally rounded into pellets in a spheronizer.

The processing of surfactants such as Gelucire® 48/16 by extrusion-spheronization is very challenging due to their low temperature of fusion. Therefore, a consequent control of the process temperature is essential. This way, pellets with a diameter of 1.4 mm and a span of 0.2 could be generated.

Systematic evaluation of the influence of material properties and punch coatings on sticking

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In pharmaceutical tableting processes, the sticking of powder to the punches is a frequent challenge. Especially drug substances may adhere to tool surfaces, causing deposits on the punches, negatively affecting powder dosing, content uniformity, and surface properties of the produced tablets. In general, sticking tendency depends on the physicochemical and mechanical interplay of powders and machine parts. It occurs, when the adhesion to the punches is greater than the cohesion of the tablet. Thin surface coatings can be used to control this sticking tendency. However, the dependencies on coating and material properties are not sufficiently elucidated, yet.

In this study, a variety of seven thin film coatings resulting from physical vapour deposition (oxides and nitrides), plasma-assisted chemical vapour deposition (SICON®), or atmospheric pressure plasma coating (MONK) were studied towards their adhesion properties with different drug substances and excipients.

On the process side, higher compression stresses lead to a higher densification, more cohesion in the tablet, and, in turn, less sticking. On the contrary, higher ejection forces are associated with lower sticking. Regarding powder properties, the general increase in sticking mass with decreasing solid density of the powder shows an interesting relation. Here, low solid density may be a surrogate for low molecular forces that cause less cohesion in compacts. Additionally, a typical trend towards higher adhesion for smaller particles was proved by higher sticking for smaller lactose particles.

SEMI-SOLID & LIQUID DOSAGE FORMS

Differential scanning calorimetry (DSC) studies on the critical micelle temperature (CMT) of poloxamers in aqueous solutions and lipid nanoemulsions

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Poloxamers (Pols) are a class of nonionic surfactants that has found various pharmaceutical applications, e.g., as emulsifiers [1]. The temperature-dependent micellization of aqueous Pol solutions is one of their most characteristic properties [2]. In the literature, however, only few data are available for the CMT of Pol solutions, and the CMT values obtained using the same method are highly heterogeneous [3]. This is partly due to differences in the molecular weight of Pols produced by different manufacturers. To accurately predict the presence of micelles in our experiments with lipid nanoemulsions, we determined the CMTs of the Pol batches used. As micelle formation is an endothermic event, aqueous solutions of different Pol samples were analyzed using DSC for this purpose. Additionally, the CMT of Pol 188 in lipid nanoemulsions was investigated to assess the possible influence of lipids in the emulsions on the CMT. Emulsions were prepared using trimyristin and medium chain triglycerides with varying concentrations of Pol 188. The concentration of free Pol 188 in the aqueous phase was quantified by measuring the refractive index in the ultrafiltrate [4]. The CMT values determined by DSC showed little difference for emulsions and ultrafiltrates.

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Comparing physico-chemical characteristics of nanoporous superalloy membranes with those of membranes established in premix membrane emulsification

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Colloidal fat emulsions can be used as carrier systems for the parenteral administration of poorly water-soluble drugs. A unique way to produce such colloidal systems with comparatively low energy input is premix membrane emulsification. The nickel-based superalloy CMSX-4 is a new and interesting membrane material for this process. Due to its high chemical and physical resistance, reusability and the high modifiability in its geometry, it offers many possibilities for the design of a new generation of membranes [1]. In order to compare this new membrane material to membranes well established for membrane emulsification, some important physico-chemical parameters of the membranes were analyzed. The wetting behaviors of the membrane materials were determined by contact angle measurement. Furthermore, the contact angle-based OWRK-method was used to calculate differences in membrane polarity. While membrane wetting with water was comparable, the new material appeared to be more polar than polymer-based membranes. To characterize their individual membrane zeta potential, the streaming potential of the different membranes was measured. During emulsification changes of particle sizes and backpressure trends were observed and compared between the membranes.

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DIGITAL MODELS IN PHARMACEUTICAL MANUFACTURING

Prediction of Solvation Free Energies for Organometallic Compounds via Molecular Dynamics Simulations

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The fight against multi-resistant strains of bacteria is an issue of global importance. In recent decades, the number of antibacterial agents discovered and brought to market has declined and failed to meet the new challenges. [a] The development of alternative classes of compounds is therefore urgently needed. Organometallic compounds based on gold complexes with N-heterocyclic carbene (NHC) ligands for instance have shown promising results [b]. Though, the accurate prediction of the solubility and other thermo-physical properties of these compounds is crucial for rational drug development.

By focusing on the solubility of organometallic compounds, we aim to improve the accuracy and predictive capabilities of computational chemistry methods. In our work, we employ molecular dynamics (MD) simulations to predict octanol-water partition coefficients of organometallic compounds [b,c,d] by deriving solvation free energies in the water-rich ($\Delta G_{solv,w}$) and the octanol-rich phase ($\Delta G_{solv,o}$). Simulations are performed with the force fields standard GAFF/RESP [e] and GAFF/IPolQ-Mod+LJ-fit [f], which has been developed in our research group, and carried out in GROMACS [g].

On the poster, we will show preliminary results for solvation free energies of selected organometallic compounds [b,c,d] for initial investigations. Our studies show improvements in the configurational space overlap and the reduction of required intermediate states along the alchemical path of the solvation process. Further, current work is also aimed at identifying suitable initial distributions of the intermediate states as function of the molecular properties of the solute-solvent pairing. The solvation free energies derived from MD simulations are compared to quantum mechanics results.

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ANALYTICS, PAT

Improving in-line measurements of model crystallizations by the careful application of an ultrasonic standing wave

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So-called radiation forces are exerted on suspended particles when subjected to an ultrasonic standing wave. This leads to various ordering effects known as ultrasonic particle manipulation. This can be used to control the whereabouts crystals of approximately one micrometer size and bigger directly within the reaction vessel. For instance, it is possible to tremendously increase the spatial concentration of crystals in the focus of a Raman spectrometer to significantly increase the signal-to-noise ration and the limit-of-detection, respectively [1].

In this work, we have further applied the technique to investigate using the ultrasonic trap soniccatch (usePAT, Vienna). Explicitly we assessed the possibility

- to keep crystals from sticking to the surface of a FTIR ATR
- to aggregate a spontaneous sample of crystals in the focal plane of an in-line microscope
- to remove crystals from the window of a probe window

These close-to-application experiments showed improvements in the sensitivity, stability, and selectivity of in-line measurements. Hence important information like when the crystallization starts, or which polymorph is forming can be acquired in a stable manner directly within the process without taking samples.

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MICROSYSTEMS FOR PHARMACEUTICAL TESTING

Development of an automated and fully sensor equipped capillary-wave microbioreactor for biopharmaceutical research

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Nowadays, new devices for fast screening and parallel testing of active pharmaceutical ingredients (APIs) are needed. Especially automated and highly parallelized microbioreactors (MBRs) with a volume in the lower microliter scale are able to close this gap. Their main advantage is the generation of a large amount of process data by integrated sensors in a small volume, which helps to save expensive media components and, at the beginning of drug development, to test the drug candidates that are still present in small quantities. Furthermore, the automation and parallelization minimize the number of work-intensive experiments.

Therefore, a new MBR with a volume of 7 µL was developed for application in biopharmaceutical research [1]. The MBR consists of a quadratic glass chip holding a sessile droplet of cultivation medium in a round cavity. The droplet is mixed by vertical oscillation inducing capillary waves on the droplets surface. Due to this technique, the MBR is called *capillary-wave microbioreactor* (cwMBR). k_La values above 340 h^{-1} and mixing times below 2 s can be achieved with this vertical oscillation [2]. For addition of liquids such as testing substances, an automated liquid handling system was integrated in the cwMBR platform. Furthermore, the processes can be characterized by inserted optical sensors for pH, oxygen and glucose. Additionally, absorbance and fluorescence can be measured for cell-based assays or detection of cell growth [3]. With the help of these sensors, a full characterization of biotechnological cultivations is possible. Moreover, the cwMBR can be applied for biopharmaceutical experiments including viability studies and phagograms.

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