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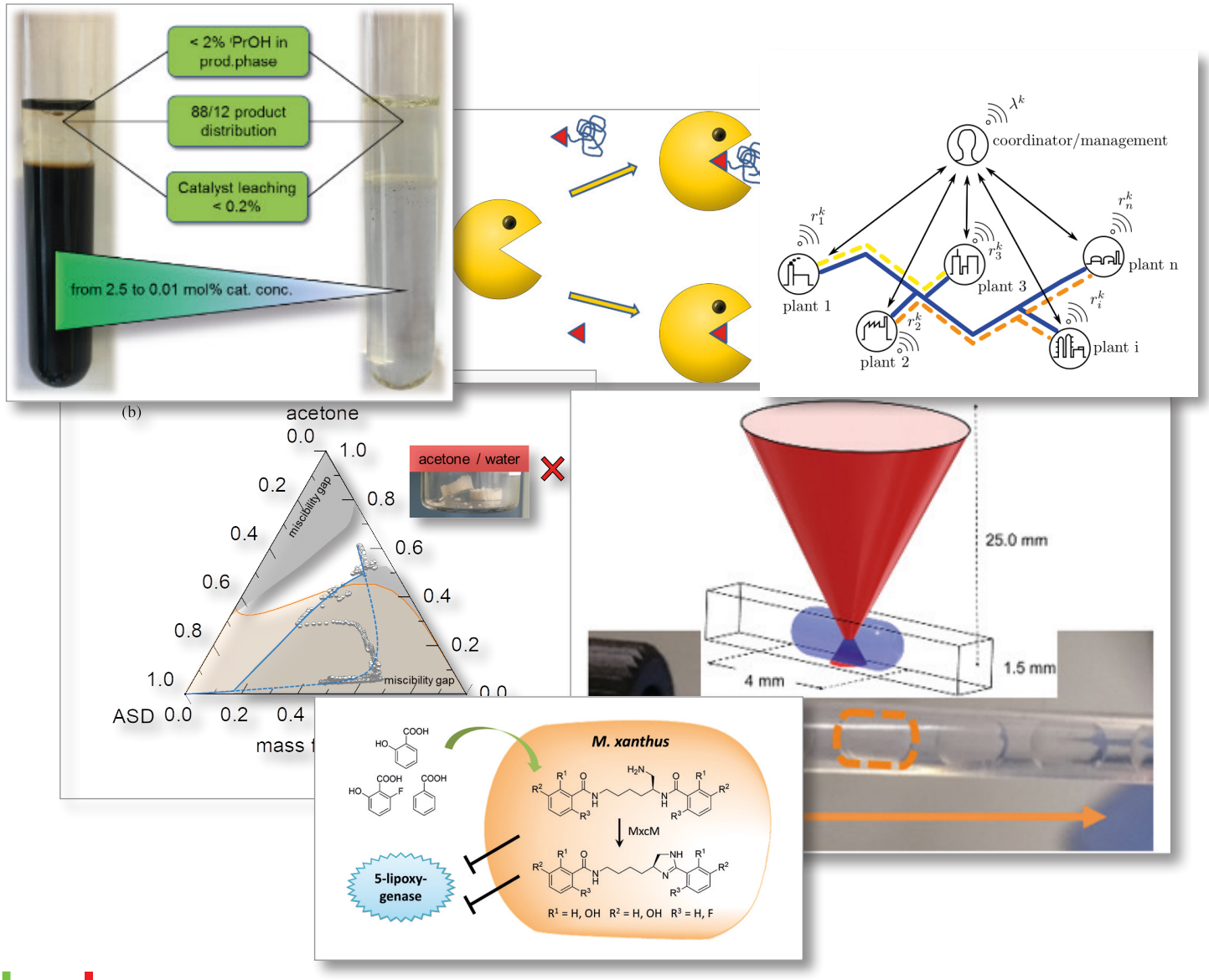
2019

SCIENTIFIC HIGHLIGHTS

Annual Report



Fakultät Bio- und
Chemieingenieurwesen

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Content

Department of BCI

Preface

Dear Reader,

I proudly present to you the Scientific Highlights of the Department of Biochemical and Chemical Engineering (BCI) of the TU Dortmund University. This year was very exciting for BCI, because we celebrated our 50th anniversary with a remarkable festivity at the Dortmunder U. It was further the year of the retirement of Prof. Górak from the Chair of Fluid Separation Technology, who has done so many great things for our department and the TU Dortmund University. We wish him all the best and particularly good health for his time after BCI. The Scientific Highlights show again the most successful scientific output of each group at BCI. We hope that you – our students, our colleagues, our scientific and industrial partners, and our funders – savor each of these Highlights and maybe this leads to new/renewed and fruitful collaborations.

Enjoy the reading

Prof. Joerg Tiller

Equipment Design (AD)

Orchestration Requirements for Modular Process Plants in Chemical and Pharmaceutical Industries

How to efficiently implement process equipment assemblies into a process orchestration layer

Lukas Bittorf, Norbert Kockmann

The increased flexibility of process plants resulting from the modularization requires an advanced strategy to supervise the distributed control systems (DCSs). The connection and coordination of multiple process equipment assemblies (PEAs) into a modular plant (MP) is called orchestration and conducted in a so-called process orchestration layer (POL). Standardized interfaces enable a seamless integration of PEAs into a MP. Current process control systems do not meet all required features regarding to interfaces and possibility of import/export of different data structures. Several aspects have to be considered when designing a POL, while the POL's several layers are particularly resulting in flexibility and reusability of modular plants.

An essential element in implementing the concept of modularization is the orchestration of the individual modules. In order to efficiently operate a modular plant, the deployed modules need to be inter-connected to each other, coordinated, and controlled in a meaningful way.

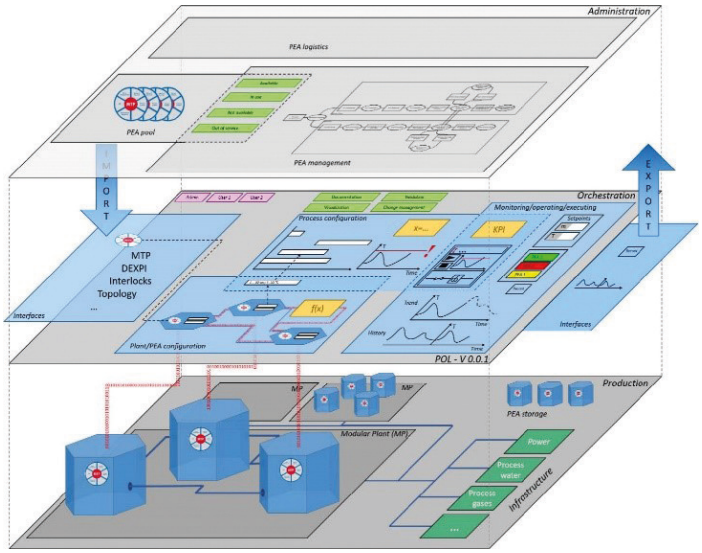

Figure 1: Complete overview of the structure of the POL in interaction with the administration layer above and the physical production layer below.

In contrast to conventional plants, the individual field level components are not directly addressed anymore – their control is now realized via services. Hence, services encapsulate the control of the individual components in order to realize the automation of the PEAs. The necessary steps for the arrangement of a modular plant can be summarized as orchestration.
Orchestration is the configuration of a specific modular plant topology with the associated interconnection of services, which are offered by the PEAs for an efficient operation of a chemical process, see Figure 1.

This includes importing descriptions of PEAs, configuring service parameters, and connecting automation and logical links. When the configuration is completed, the existing services can be either started manually or run automatically as part of a recipe. Herein, interdependencies between services must be considered during the configuration. After completion of the orchestration, the modular process plant is ready for operation.

The fundamental category of the POL consists of standardized interfaces. Via these interfaces, the necessary data can be imported into the POL and the resulting information is made available to other systems. Data can be exchanged for example with external engineering programs, with other data science applications for the evaluation of structured data, or even between different POL systems. The main part of the automation interface, the module type package (MTP), is specified in the technical guideline VDI 2658. Parallel, a guideline VDI 2776 specifies the process engineering view of modular plants.

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A. Klose, S. Merkelbach, A. Menschner, S. Hensel, S. Heinze, L. Bittorf, N. Kockmann, C. Schäfer, S. Szmais, M. Eckert, T. Rüde, T. Scherwietes, P. da Silva Santos, F. Stenger, T. Holm, W. Welscher, N. Krink, T. Schenk, A. Stutz, M. Maurmaier, K. Stark, M. Hoernicke, S. Unland, S. Erben, F. Kessler, F. Apitz, L. Urbas, Chem. Eng. Technol. 2019, 42, No. 11, 2282-2291 (2019).

Microfluidic Devices Manufactured by Reactive Ion Etching

A new manufacturing technique for microreactors

Jens Bobers, Maurice Hesselmann, Arndt-Christian Schneider, Jakob Zimmermann, Norbert Kockmann

Microstructured devices provide improved control of strong exothermic or mixing sensitive chemical reactions due to high surface-to-volume ratio and increased heat and mass transfer rates. Finding a manufacturing process for small devices with structures in the range of micrometers is a challenge for obtaining high spatial resolution and good surface quality. Reactive ion etching is a high-resolution technique offering adjustable surface characteristics. In this highlight, we present a manufacturing process for microfluidic devices based on reactive ion etching of highly chemical resistant polyimide foil as substrate.

The aim of this work was the precise structuring of a chemical and thermal resistant material, which is needed for the application as chemical reactor, with reactive ion etching (RIE) as manufacturing technique. A general scheme of the RIE process is shown in Figure 1. Polyimide (PI) is a chemical stable, heat resistant and electrically insulating high performance heterocyclic polymer, which is mainly used for flexible microelectronics and can be found in nearly every microelectronic device. PI foils with a thickness of 125 µm were used as substrate material for the microfluidic devices.

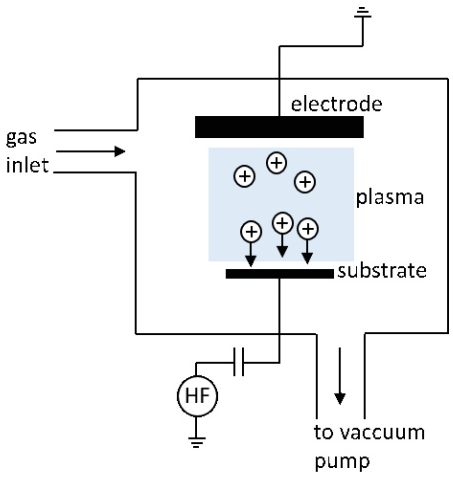

Figure 1: Simple schematic representation of the reactive ion etching process with PI foils as substrate in the etching chamber with a high frequency HF electrical field generating the etching plasma.

Multiple parameters influence the quality of the etching process such as gas composition containing sulphur hexafluoride, argon, and oxygen, the pressure inside the etching chamber as well as gas flow rates. The Design of Experiment (DoE) methodology allows the investigation of the influence of each parameter and their interaction on the surface roughness after the etching and the overall etching rate. A 2^4 full factorial designed experiment was performed as four factors, three volumetric gas flow rates and the internal pressure of the etching chamber, on two different levels were investigated.

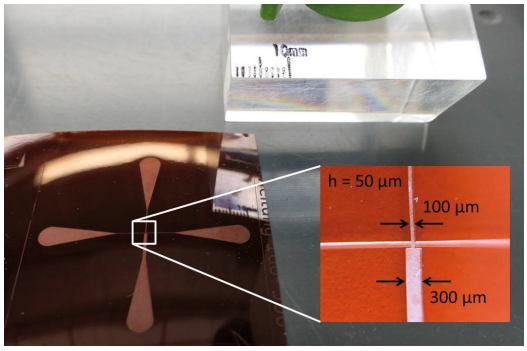

Figure 2: Polyimide-based microfluidic device for droplet generation manufactured by reactive ion etching with optimized parameters.

With optimized parameters the etching rate was increased up to 0.714 µm·min^{-1}. The mean surface roughness was measured as 0.540 µm. Figure 2 shows the results of the etching process with optimized etching parameters.

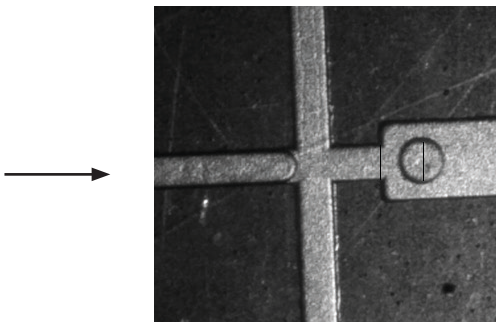

Figure 3: Water droplets in silicon oil inside a polyimide-based microfluidic device.

The device was successful applied on the generation of water droplets with diameters from 150 to 230 µm in a continuous silicon oil phase as shown in Figure 3.

Publications:
J. Bobers, M. Hesselmann, A.-C. Schneider, N. Kockmann, 17th International Conference on Nanochannels, Microchannels, and Minichannels, ASME-ICNMM 2019, DOI: 10.1115/ICNMM2019-4208.

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In-situ Monitoring of Chemical Reactions and Polymerization in Microreactors

Cost efficient and effective methods to measure reaction kinetics and optimize chemical reactions

V. Fath, T. Klement, Thorsten Röder, Norbert Kockmann

Studying chemical reactions on lab scale requires modern equipment, integrated sensors, and sophisticated numerical analysis routines. Various own investigations embraced highly reproducible polymerization monitoring of polyacrylic acid as well as organolithium reactions. The results were taken for scale-up considerations as well as for the further investigation of important side reactions and prior unknown dissolution dynamics of butyl lithium BuLi.

A millistructured reactor and spectroscopic setup for contactless kinetic measurements in oscillating droplets is presented in this contribution. The polymerization of acrylic acid serves as a model reaction. Design and construction of the reactor focus on the optical access for Raman measurement, shown in Figure 1, the nearly isothermal behavior, and the preservation of droplets during long-term reactions with a high increase of viscosity. Another key aspect is the possibility of full automation at a later stage.

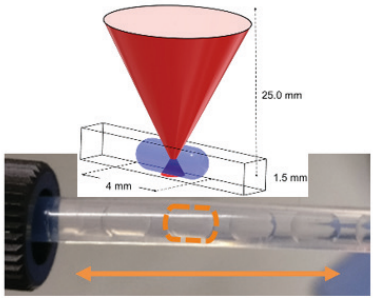

Figure 1: Schematic representation of the focus of the laser in the droplet and typical flow in the FEP capillary. Working distance between optical lens and droplet center is 25 mm, with a spot size of 150 mm.

Main focus of preliminary investigations is on the reactor setup to guarantee ideal conditions (necessary mixing performance, isothermal behavior, defined reaction start, etc.) as far as possible for the reaction while measuring with high frequency and accuracy. The reactor enables generating and preserving droplets over the reaction time or slugs and measuring them by using a Raman focus probe.

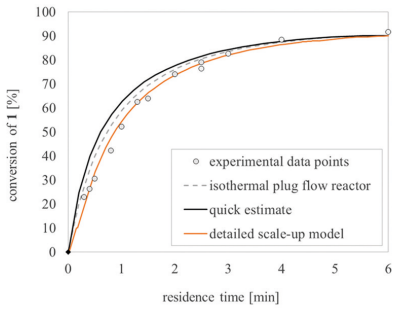

Figure 2: Comparison of the quick estimate and detailed scale-up model and isothermal plug flow reactor. Comparison of conversion profiles at a coolant temperature of −25 °C.

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In-situ monitoring of lithiation reaction reveal not only reaction kinetics, but also dissolution dynamics of reagents with solvent. This work includes model-based scale-up predictions of a deprotonation reaction with n-butyllithium of high industrial relevance. A complete process development was developed for its transfer from the lab to the pilot scale. Two different model-based scale-up approaches were successfully applied in order to represent experiments at larger scale (Figure 2). For the conversion, the quick estimate (a diabatic plug flow reactor with a constant mixing time in a Kenics static mixer) is sufficient.

From these measurements, it could be shown that a complex reaction mechanism is involved in the synthesis of a highly reactive, nonisolable, lithiated component. Based on several kinetic approaches studied, a possible mechanism based on the formation of BuLi aggregates in tetrahydrofuran is postulated (Figure 3).

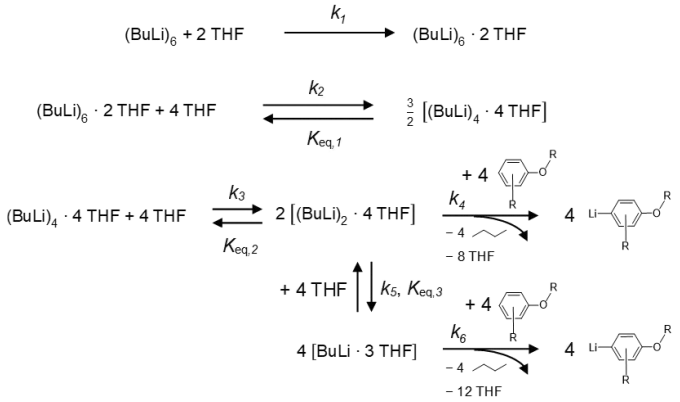

Figure 3: Possible reaction mechanisms for classical synthesis starting from hexameric BuLi formation.

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Publications:
V. Fath, S. Smaisz, P. Lau, N. Kockmann, T. Röder, Org. Proc. R&D, 23(9), 2020-2030, 2019.
T. Klement, N. Kockmann, T. Röder, Chemie Ingenieur Technik, 91(5), 651-656, 2019.
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Microcalorimeter Determines Mixing Time of Instantaneous Reactions

Felix Reichmann, Timothy Aljoscha Frede, Norbert Kockmann

One of the most decisive and basic processes during chemical transformation is the mixing of reactants. Mixing time scales are derived from heat flux profiles for an instantaneous and exothermic reaction in a commercially available microreactor. A continuous reaction calorimeter, based on numerous heat flux sensors, is used to record spatial resolved heat flux profiles in steady state. Results display a decrease in mixing time at increased volumetric flow rates and energy dissipation rate. Additionally, the passive micromixer is evaluated regarding its mixing efficiency.

A continuously operated reaction calorimeter based on Seebeck elements (SE) as heat flux sensors, a locally resolved heat flux profile is recorded for the microreactor in steady state, where the peak position gives the location of main reaction progress. The determination of mixing time is a “by-product” of the thermokinetic measurements and presents an easy approach with small expenditure. Moreover, this method can be applied to any reactor material regardless of its transparency. Color change of a pH indicator in an acid-base reaction and respective peak positions in the heat flux profiles are compared for validation.

In general, total values of heat flux signals increase with higher volumetric flow rates due to a larger amount of reactants fed into the microreactor and more heat generation (see Figure 1).

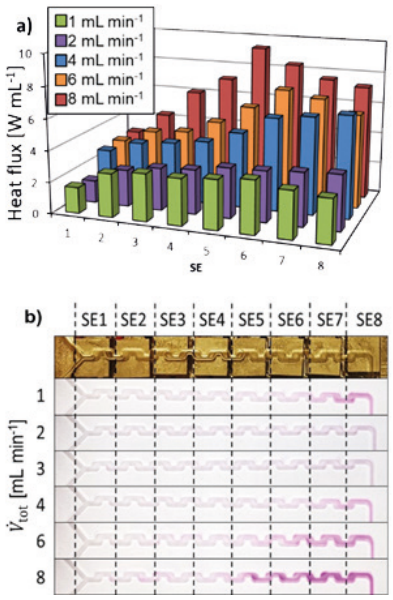

Figure 1: a) Spatially-resolved specific heatflux signals for neutralization reaction of 1 M HCl and 1.1 M NaOH at varied flow rates. b) Optical observation of pH indicator color change at varied flow rates for neutralization reaction.

For the smallest employed volumetric flow rate, a heat peak can be identified between SE7 and SE8. With *Re* = 21, mixing is assumed to be dominated by diffusive regime. Real flux peaks can be detected from a flow rate of 6 mL min^{-1} (*Re* = 129 and *Dn* = 58) and upwards, with the peak being shifted upstream toward the inlet for higher flow rates. Dean vortices become stable for this *Dn* range and mixing mechanism therefore transitions to convective regime and a heat flux peak can be detected above SE6 (see Figure 1a). After the reaction is complete, heat flux signals decrease as generated heat is removed from the reaction mixture through the reaction walls and other parts of the calorimeter. Additionally, the neutralization enthalpy was measured. The determined values deviate less than 1 % from the literature value for flow rates of 1, 6 and 8 mL min^{-1}, which proves full conversion of the reagents.

Mixing time scales were determined with channel lengths until complete mixing (heat flux peak location) and average flow velocities. Figure 2a displays the obtained mixing times for the volumetric flow rates which led to full conversion within the microreactors (diamond symbols).

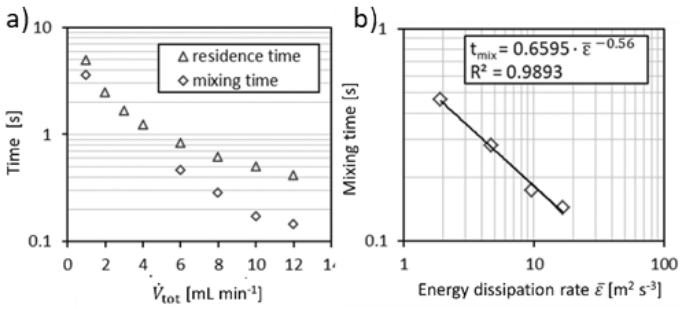

Figure 2: a) Mixing time over flow rates that gave full conversion within the microreactor. b) Mixing time scale plotted over energy dissipation rate with power law trend line that fits the data.

The relationship between mixing time scale and energy dissipation rate was derived by a decreasing trend line following a power law, which is known from mixing time studies in microreactors (see Figure 2b). Thus, the intensified mixing compared to conventional reactors illustrates the applicability of the studied microreactor for fast reactions.

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Solid-Liquid Suspension Handling - Key Variable for Continuous Crystallization in Small-Scale Devices

Investigations on homogeneous suspension for continuous cooling crystallization

Mira Schmalenberg, Lukas Hohmann, Norbert Kockmann

Increasingly specific customer requirements and tailor-made products drive process development. In order to be able to produce small quantities, the importance of small-scale, continuously operated equipment is increasing in the specialty, fine chemical and pharmaceutical industries. When using solid material, e.g. during crystallization, it is essential to avoid clogging in these devices to enable continuous operation. For this reason, a homogeneous suspension within the devices is the key for ensuring stable and robust operation.

Manufacturing of fine chemicals and pharmaceuticals often comprises the handling of solid/liquid suspensions both in upstream and downstream processing. In order to ensure continuous operation even with small apparatus, it is essential to avoid clogging.

For a plug flow crystallizer in a coiled flow inverter (CFI) design an empirical correlation were developed to predict which suspension mass flow rate is necessary to ensure a homogeneous suspension flow (see Figure 1). For this, it must be considered what proportion of solids is present in the suspension and what size the particles have. In addition, the properties of the apparatus are important, here e.g. the inner diameter of the tube. Since the correlation is based on dimensionless parameters, such as the Froude number, a transfer to other systems is possible.

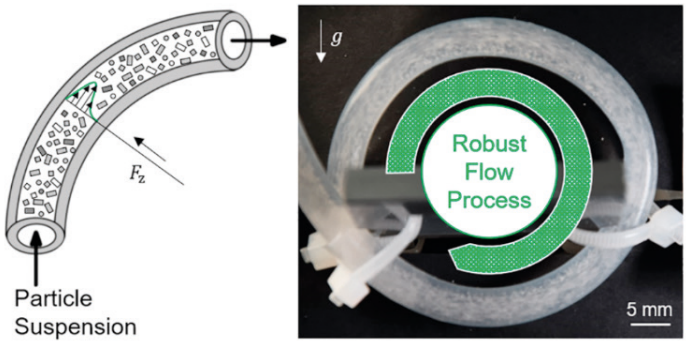

Figure 1: Coiled tube with homogeneous suspension flow; schematic (left), photo (right).

However, the Froude number is not only used for characterization in tubes/pipes, but can also be used for stirred vessels. Even in stirred tanks and during continuous operation it is important that feed inlets and product outlets do not block. For this reason, the suspension behavior was determined for a newly designed small-scale draft tube baffle (DTB) tank (see Figure 2). This stirred tank and its characterization of the suspension behavior serves as a basis for the construction of an improved miniaturized DTB crystallizer, which classifies the particles within and the particle size to be discharged can be influenced by adjusting the stirrer speed.

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Figure 2: Miniaturized DTB tank during suspension behavior investigations; filled with 1 L suspension and a solid weight fraction of 0.01.

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3D Investigation of Liquid/Liquid and Liquid/Gas Interfaces using Micro-Computed Tomography

Non-invasive, high resolution and 3D measurement technique for a better understanding of multiphase processes

Julia Schuler, Norbert Kockmann

For a better understanding of multiphase phenomena in miniaturized applications, such as the generation of monodisperse droplets and bubbles in mini- and microchannels, experiments are mainly assisted by the use of optical cameras. However, for a deeper understanding of the ongoing physics, a three dimensional measurement technique is desired. Micro-computed tomography is a three-dimensional, non-invasive imaging technique offering resolutions down to 4 µm. While tomographic imaging already serves as a promising tool for multiple applications in process engineering research, using CT in mini- and microfluids is still challenging.

This work shows the entire workflow for imaging static liquid/liquid and liquid/gas interfaces, from image acquisition, Figure 1a), and reconstruction of the data to a 3D dataset to an automated analysis procedure. The potential of the methodology is demonstrated for static liquid/liquid and gas/liquid interfaces layered in thin polymer tubes, see Figure 1b) and c).

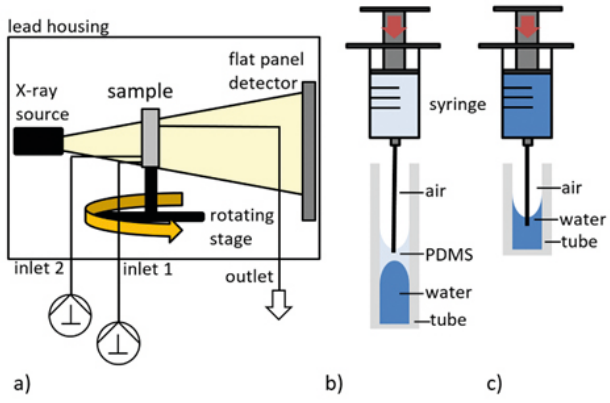

Figure 1: a) Schematic of the experimental set-up for tomographic imaging, the sample is rotated during image acquisition. b)-c) Generation of static multiphase interfaces using a syringe. [1]

Some resulting interfaces are shown in Figure 2. The interfaces were investigated regarding contact angles at the solid tubing and interface morphology. Using the proposed method allowed the identification of the influence of gravity on the formation of a liquid polydimethylsiloxane/air interface. Contact angles were compared to literature data showing good accordance. The present work builds the basis for future investigations. This will incorporate the extension of the methodology to the investigation of multiphase flow and mass transfer phenomena in miniaturized equipment.

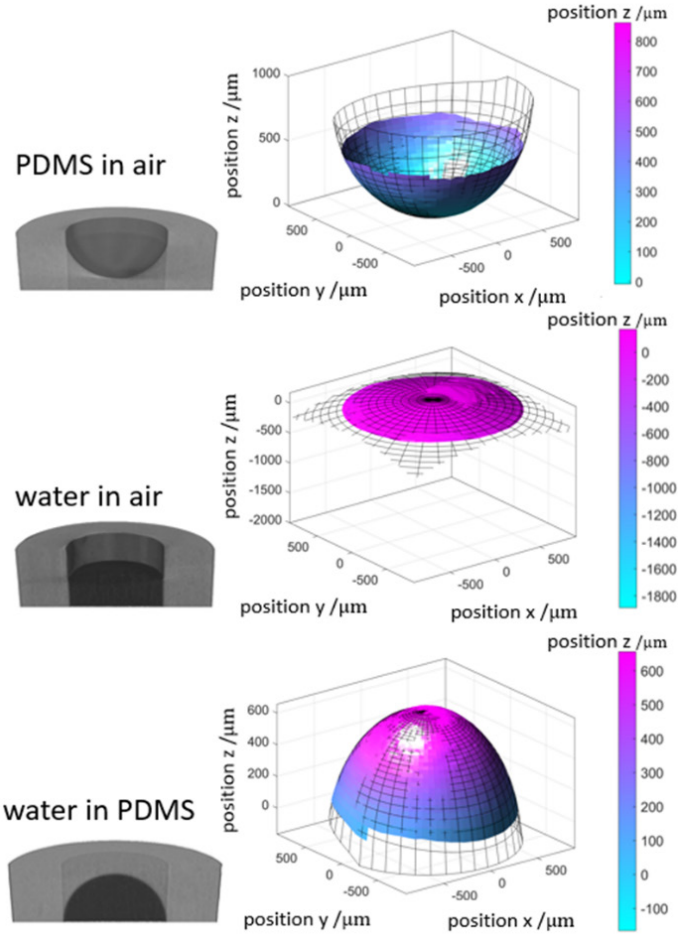

Figure 2: 3D representations of PDMS/air, water/air, and water/PDMS interfaces. [1]

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Publications 2019 - 2017

2019

Peer Reviewed Journal Papers

- V. Fath, S. Smaisz, P. Lau, N. Kockmann, T. Röder
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  Orchestration Requirements for Modular Process Plants in Chemical and Pharmaceutical Industries
  Chem. Eng. & Technol., 42(11), 2282-2291, 2019; doi.org/10.1002/ceat.201900298

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  Suspension Flow Behavior and Particle Residence Time Distribution in Helical Tube
  Chem. Eng. J., 360, 1371-1389, 2019; doi.org/10.1016/j.cej.2018.10.166

Peer-reviewed conference papers

- J. Bobers, N. Kockmann
  Development of a Manufacturing Process For Polyimide-based Microstructured Devices Using Reactive Ion Etching
  ASME-ICNMM2019-4208, St. John´s, Canada, June 23-26, 2019

- J. Bobers, N. Kockmann
  Non-invasive Temperature Measurement For Polyimide-based Microstructured Devices
  ASME-ICNMM2019-4207, St. John´s, Canada, June 23-26, 2019

- N. Kockmann, W. Krieger, M. Schmalenberg
  Design and Scale-up of Modular Capillary-Flow Inverter Reactors with Narrow Residence Time Distribution
  ASME-ICNMM2019-4237, St. John´s, Canada, June 23-26, 2019

- J. Schuler, N. Kockmann
  Investigation of multiphase interfaces in small channels using micro CT
  ASME-ICNMM2019-4203, St. John´s, Canada, June 23-26, 2019

Publications 2019 - 2017

2018

Peer Reviewed Journal Papers

- N. Kockmann
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Plant and Process Design (APT)

(Non-)Predictability of the Surface Activity of Proteins Based on their Molecular Features

About the importance of hydrophobicity, amphilicity and flexibility for the surface activity of proteins

Jörg Koop, Juliane Merz, Gerhard Schembecker

The surface activity of proteins has been known for a long time and is used predominantly in food industry for aerated products, emulsions, and foams. The ability of proteins to form and stabilize foam is also usable in bioprocess engineering for in situ product removal from gassed bioreactors. Another application is foam fractionation, a purification method for surface-active molecules. However, in order to predict the performance of such processes, it would be highly desirable not to entirely depend on experiments to determine the surface activity of proteins. Thus, a set of model proteins was analyzed on theoretical basis to find correlations between their molecular features like hydrophobicity, amphilicity, or accessibility of amphiphilic structures and their surface activity on macroscopic level.

Surface activity is the capability of adsorbing at an interface and stabilizing it. In the particular case of air-water interfaces, surface-active molecules in gassed solutions lead to the formation and stabilization of foam.

Analogously to artificial surfactants, like soaps or detergents, the surface activity of proteins is caused by their amphilicity, which is based on the hydrophilic and hydrophobic character of the amino acids. Because the hydrophobic amino acids adsorb at the interface, it seemed most reasonable to focus on the hydrophobicity of the amino acid residues. In our study, we found that the average hydrophobicities of the proteins investigated did not differ significantly from each other. Even hydrophobins, proteins designed by nature to exhibit outstanding surface activity, showed no trend in that feature. Although it was assumed that both were highly hydrophobic, that was true for one protein only, and the other was hydrophilic. Then, the focus was on the amphilicity of the secondary structure. The so-called hydrophobic moment is a measure of the amphilicity of secondary structure elements (see Figure 1).

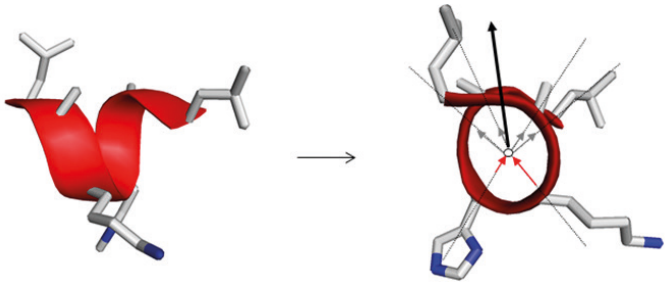

Figure 1: Illustration of the hydrophobic moment of an α-helix (black arrow). The amphilicity results from hydrophobic residues (grey arrows), and hydrophilic (red arrows), which are located on opposing sides on the structure.

Structures with a high hydrophobic moment, therefore being highly amphiphilic, can be assumed to exhibit a strong driving force to adsorb at the air-water interface. The water-repelling hydrophobic residues are then not surrounded by water anymore, while the water attracting-hydrophilic structures are still in bulk liquid. However, the presence of those highly amphiphilic structures or the extent of amphilicity did not correlate with the macroscopic behavior of the proteins investigated. Thus, it was investigated whether the amphiphilic structures are accessible without extensive refolding processes of the protein.

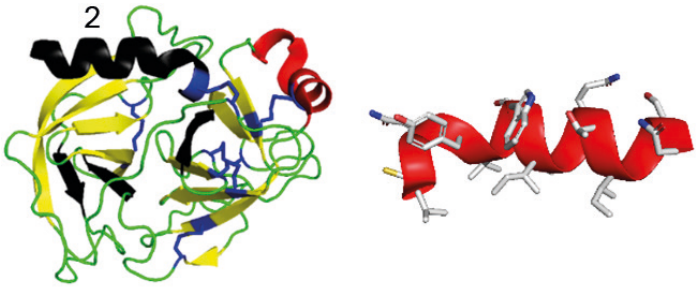

Figure 2: Cartoon representation of the protein trypsinogen. The top 4 amphiphilic structures are colored black. The second amphiphilic structure (2) is accessible only.

The accessibility of amphiphilic elements is exemplarily shown for the protein trypsinogen in Figure 2. However, even by including the tertiary protein structure, it was not possible to explain the actual macroscopically measurable surface activity. Another less surface-active protein was papain, and it had more equally amphiphilic secondary structure elements. That gave rise to doubts that, based on theoretical analysis, any conclusions or even predictions can be made for the surface activity of proteins.

On the other hand, the conditions (pH and ionic strength) leading to a high surface activity where often the same as those for the so-called molten globule state (MGS). That is a conformation with a weakened tertiary protein structure, therefore being more flexible. However, the MGS itself is, like the surface activity, determined by macroscopic observations individually for each protein. Thus, it is not suitable for prediction of surface activity.

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Publications:
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Correlating Stationary Phase Retention in Centrifugal Partition Chromatography

A first step in simplifying solvent system selection for CPC operation

Angela Fromme, Felix Funke, Juliane Merz, Gerhard Schembecker

Centrifugal Partition Chromatography (CPC) is a promising downstream technique to satisfy the increasing demand for high purity products. Due to the two liquid phases used, the operational mode of the CPC equals a multistage extraction but enables separation efficiencies comparable to packed-bed chromatography processes. During CPC operation, the individual influence of the retention of the stationary phase, the coalescence, and the dispersion of the mobile phase in the chambers of the rotor used must be understood to select appropriate solvent systems and reach high separation efficiencies. In this study, an optical measurement system was used to investigate the influence of the physical properties of the Arizona solvent systems on the stationary phase retention in descending mode.

The aim of this work was the development of a correlating function including all influencing parameters, which can be used to predict the stationary phase retention (Sf*) inside the CPC. Influencing parameters are the operating parameters used, which can be expressed by the fluid velocity at the inlet (v) and the relative centrifugal force (RCF) and the physical properties of the solvent system used, including density (ρ), viscosity (η), and interfacial tension (γ). By performing a dimensional analysis, dimensionless numbers combining the influences of the operating parameters and the physical properties of the mobile (m) and the stationary phase (s) could be determined. These dimensionless numbers were the Capillary number (Ca) and the Morton number (Mo) described by equations 1 and 2.

$$Ca = \frac{\eta_m \cdot v}{\gamma} \quad (1)$$

$$Mo = \frac{RCF \cdot g \cdot \eta_m^4 \cdot (\rho_m + \rho_s)}{\gamma^3 \cdot \Delta\rho^2} \quad (2)$$

According to the definition of dimensional analysis, these numbers combine the influences on Sf*. However, dimensional analysis does not provide any information about the function describing the relationship between the dimensionless numbers. This function can only be obtained experimentally. Hence, the next step was the search for a suitable correlation of Sf* for different solvent systems based on a function including Ca and Mo with the help of experimental investigations.
For the determination of Sf* an optical measurement system, enabling the investigation of the fluid dynamics inside the CPC, was used. Sf* was determined for the aqueous-organic Arizona solvent systems A, D, H, J, K, N, R, U, X, and Z under different operating conditions in descending mode operation. In Figure 1 the experimental results are presented in dependency of the dimensionless numbers Ca and Mo.

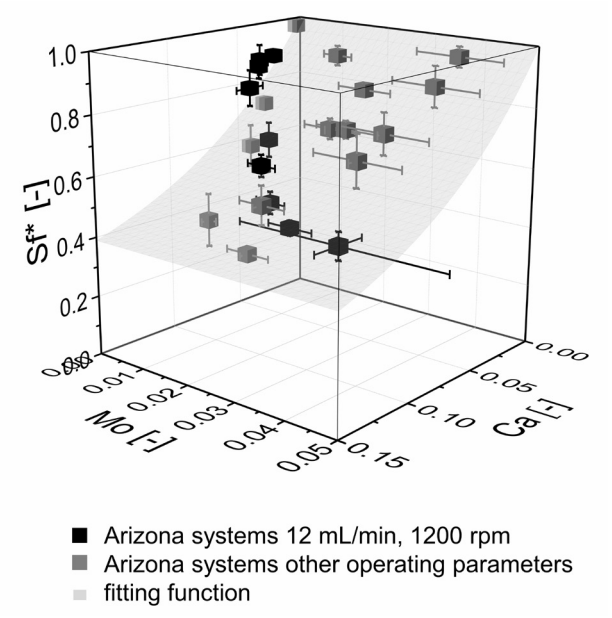

Figure 1: Stationary phase retention (Sf*) of the investigated Arizona solvent systems measured after 30 min at different operating parameters at 25 °C in dependency of the Capillary number (Ca) and the Morton number (Mo).

Using the experimental results, a fitting function, described by equation 3, could be gained.

$$Sf^* = 0.225 + 0.775 \cdot exp\left(\frac{-Mo}{2.390 \cdot 10^{16}} + \frac{-Ca}{0.097}\right) \quad (3)$$

Analyzing the function, it can be seen that the stationary phase retention is high for low values of Ca and Mo, whereas the influence of Mo is neglectable in the parameter space investigated.
The gained function can be used to predict Sf* for different aqueous-organic solvent systems at different operating conditions.

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Biomaterials and Polymer Science (BMP)

Shape-Memory Effect of Biocompatible PEtOx-Hydrogels

New insights on the LCST behavior of hydrogels

Dominik Segiet, Thomas Raidt, Hatay Özdem, Sebastian Weckes, Frank Katzenberg, Joerg C. Tiller

Shape memory polymers are an important class of smart materials with a broad range of applications. They are usually prepared by cross-linking established mass polymers, such as polyethylene or natural rubber. In order to broaden the usefulness of such smart materials, new materials with new polymers are required. An interesting class of thermoplastics for realizing shape-memory polymers are poly(2-alkyl-2-oxazoline)s (POx), because they offer a variety of exceptional properties. Poly(2-ethyl-2-oxazoline) (PEtOx) for example exhibits a solubility in water and hydrophobic solvents, a lower critical solution temperature (LCST), and biocompatibility coupled with a glass transition temperature T_g *above room temperature. Especially the biocompatibility is essential for potential further medical applications. This study shows the first example of a shape memory material prepared with PEtOx.*

Commercially available PEtOx was successfully crosslinked by using a mixture of dicumyl peroxide and triallyl isocyanurate and the critical degree of crosslinking at which a network is formed was determined to 0.27%.

Expectedly, critically crosslinked PEtOx (x-PEtOx) is easily and highly stretchable and, thus, is capable of storing the highest strain of 650% of all considered degrees of crosslinking. The materials x-PEtOx were programmed by either heating them above T_g, stretching, and then cooling to room temperature or by swelling in water, stretching, and then drying. The trigger temperature T_{trig} of x-PEtOx, where the stretched material returns to its original shape, was found to be 68 °C for all dry networks. Moreover, it was found that the T_g of x-PEtOx is strongly influenced by water and decreases with increasing water uptake. A thermal triggering of samples was therefore possible by applying only water or a relative trigger humidity RH_{trig} above 40%. Independent of the kind of triggering, the degree of cross-linking and the amount of stored strain, all considered x-PEtOx´ networks fully recovered their permanent shapes.

Since T_{trig} correlates to the T_g of the sample and therefore ambient relative humidity *RH* at which the sample is stored, when the programmed sample is stored below RH_{trig}, it was possible to gradually decrease T_{trig} by air moisture (see Figure 1).

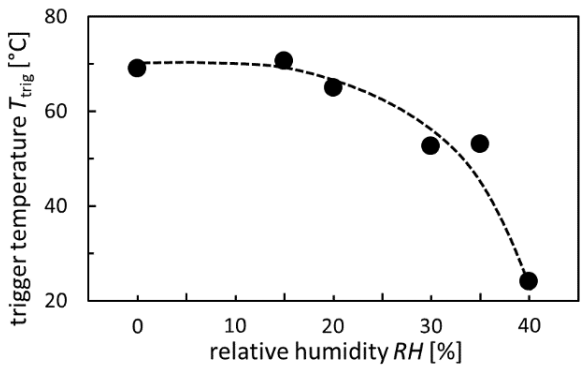

Figure 1: Trigger temperature of critically cross-linked x-PEtOx in dependence on the relative humidity.

Besides thermal programming, moisture swollen x-PEtOx at a temperature of 25 °C and a relative humidity *RH* of 50%, were found to be similarly stretchable as dried PEtOx networks above T_g at 80 °C. Moreover, after lowering the ambient *RH* below RH_{trig} a full fixation of the applied programming strain in the temporary shape was observed. Since T_{trig} significantly depends on ambient *RH*, an x-PEtOx shape-memory polymer is applicable as sensor/actuator that is capable of being programmed and triggered by applying both, temperature and *RH* (see Figure 2).

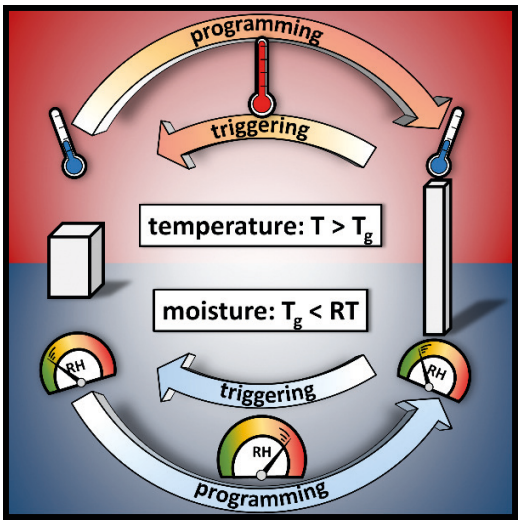

Figure 2: Diagram showing the possibilities for programming and triggering x-PEtOx.

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Self-Deactivating Antibacterial Polymers

Environmentally friendly biocides that act fast and loose their activity upon partial hydrolysis

Christian Krumm, Lena Benski, Joerg C. Tiller

Biocides are ubiquitous in many products of daily life. Unfortunately, they are polluting the environment and lead to resistant bacterial strains due to prolonged activity, which is one of the biggest problems in medicine. The ideal biocide would be a chemical compound that kills microbes quickly and is then degraded and deactivated. One possibility to achieve this is the design of antibacterial polymers that can be hydrolyzed in water and lose their activity even before they are fully degraded. Here, we present polyionene esters that are capable of killing bacteria within minutes and are hydrolyzed and thus deactivated within hours to days depending on the composition.

In order to implement a degradable functional group in the structure of hydrophilic polycations different bifunctional acyl chlorides were reacted with different tertiary amino alcohols to give tertiary diamines with two inner ester functions, which can serve as monomers for the synthesis of polycations. The polycation synthesis was performed by reacting these monomers with an equimolar amount of 1,4-dibromobutene in acetone.

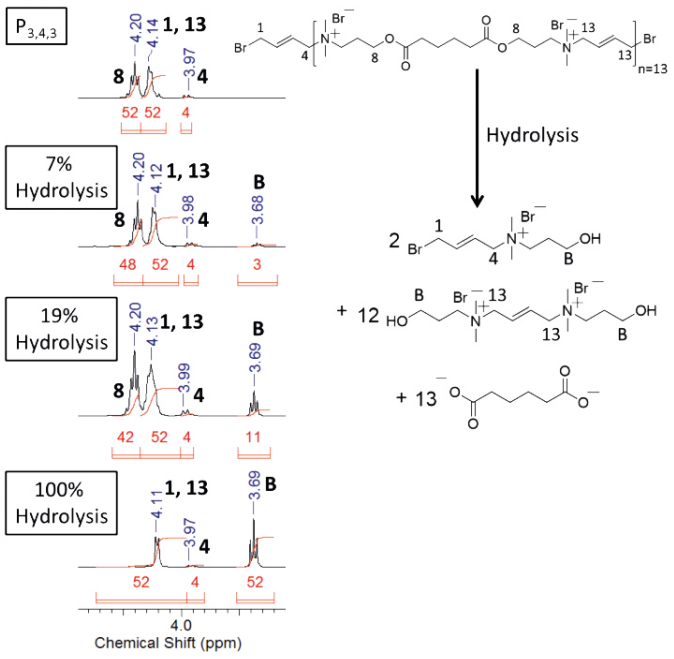

Figure 1: Sections of ^{1}H-NMR spectra of a partially hydrolysed PBI ester for the determination of degree of hydrolysis.

The hydrolysis of the polymers was followed by ^{1}HNMR spectroscopy (Figure 1). Depending on the number of methylene groups in the backbone and the pH of the surrounding solution, the degradation could be observed within 1h to several days.
The PBI esters are antibacterially active against a wide range of bacterial strains and were found to quickly kill these cells within 1 to 10 min.

The structure of the polymers also controls the deactivation mechanism. While the more hydrophilic polymers require hydrolyses of only 19 to 30 % of the ester groups to become practically inactive, the more hydrophobic PBI esters require up to 85 % hydrolysis to achieve the same result. This is most likely due to the fact that the hydrolysis introduced satellite groups at the polymer fragments, which diminish the antibacterial activity. Thus, depending on the environmental conditions and the chemical nature, the PBI esters can be active for only 20 min or for at least one week (Figure 2).
The PBI esters were shown to not disrupt blood cells showing that their mechanism of action is different from typical amphiphilic polycations that are membrane disruptive.

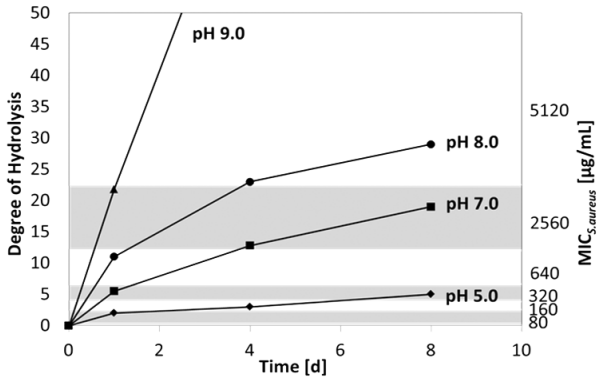

Figure 2: Hydrolysis of the PBI esters shown in Fig. 1 in different aqueous buffer solutions. The $MIC_{S.aureus}$ values of the partially hydrolyzed polymers were determined and the respective values are marked as areas (alternating grey/white) in the diagrams.

We have shown that PBI esters are highly active broad-band polymeric biocides that kill bacterial cells within minutes. They do not induce hemolysis, but are toxic to human mesenchymal stem cells. The polymers degrade in aqueous media and become inactive and significantly less toxic even upon partial degradation. The inactivation in neutral media is complete after 1 day and takes only 20 min for the most hydrophilic PBI ester in buffer at pH 10. Thus these polymers are interesting fast acting biocides with a potentially low environmental impact.

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Competitive Enzyme Inhibitors Attached to a Polymer Terminus

A weak laccase inhibitor is activated by a factor of 30 when attached to a poly(2-oxazoline) chain

Montasser Hijazi, Christian Krumm, Lena Benski, Joerg C Tiller

Enzyme inhibitors are essential in medicine (half of all pharmaceuticals are enzyme inhibitors), but have also great importance in agriculture, biosensing, and biotechnology. Increasing their activity and selectivity is one important task in modern biosciences. The combination of enzyme inhibitors with enzymes has been successfully used to render their bioavailability, release or local concentration. In some cases multivalent binding to nanoparticles of polymer aggregates has been shown to improve such bioactive molecules. Here, we follow the concept of binding a weak inhibitor (iminodiacetate, IDA) molecule for the important enzyme laccase onto a biocompatible, water-soluble poly(2-oxazoline) (POx) chain. This concept was found to be quite efficient in activating the inhibitor and simultaneously stabilizing the enzyme.

According to the concept depicted in Figure 1, an enzyme inhibitor attached to a polymer chain end could be activated by the fact that the polymeric tail additionally blocks the active site of the enzyme. Also, the inhibitor can bind near the active site and would still be active due to its bulky tail. This might increase the variability of potential enzyme inhibitor. On the downside, the polymer tail might hinder binding to the active site due to sterical hindrance and it will also induce diffusion limitations.

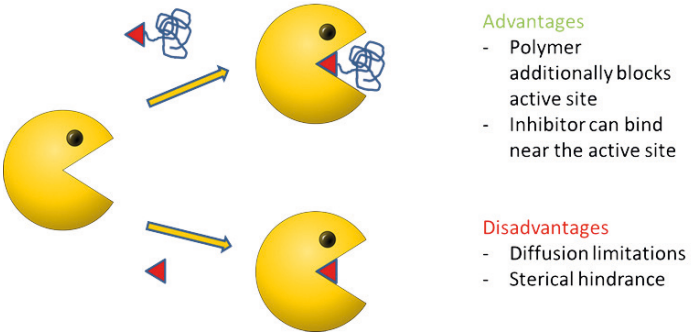
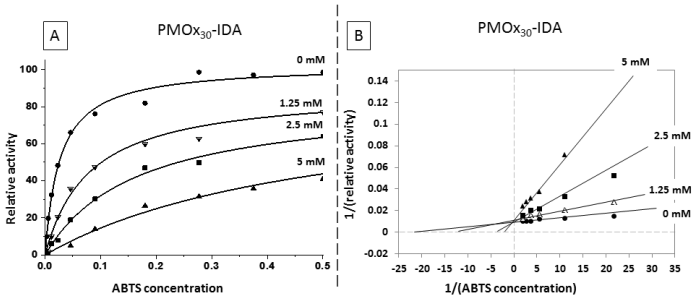


Figure 1: Binding concept of a competitive enzyme inhibitor attached to a polymer.

The established polymers based on poly(2-methyl-2-oxazoline) (PMOx) and poly(2-ethyl-oxazoline) (PEtOx) were terminated with an IDA group at one or both terminals, respectively.

The inhibition of laccase was tested using ABTS as substrate in the presence of different PMOx-IDA concentrations. The Michaelis-Menten plots reveal that the increase of PMOx30-IDA concentration increases also the Michaelis constant Km from 0.026 mM of the native enzyme to 0.5 mM at 5 mM of $PMOx_{30}$-IDA, while no significant change of the maximum oxidation rate V_{max} occurs. This is typical for a reversible, competitive inhibition mechanism for the monofunctional PMOx. The Lineweaver-Burk plots clearly confirmed that the competitive inhibition mechanism given in Figure 2, right, can describe the inhibition of the laccase by PMOx-IDA polymers. The inhibition of the polymer is 30 times higher than IDA alone. Diluting the polymers/enzyme mixtures resulted in full activity of the enzyme, proving the inhibition is indeed reversible. It could further be shown that the double side polymer IDA-PEtOx-IDA is a dead-end inhibitor for laccase, e.g. it inhibits the enzyme to 100 %.



	Km (mM)	Vmax %
Native	0.026± 0.003	100
1.25 mM (PMOx-IDA)	0.079± 0.01	90 ± 4
2.5 mM (PMOx-IDA)	0.163± 0.02	85 ± 5
5 mM (PMOx-IDA)	0.506± 0.11	89 ± 10

Figure 2: Kinetics and kinetical constants of laccase activity in the presence of varying concentration of the inhibitor PMOx-IDA and the substrate ABTS.

Laccase is a rather fragile enzyme, which quickly loses its activity during storage, particularly in aqueous solution. While the enzyme loses its activity nearly completely after one week of storage in aqueous solution at room temperature, POx-IDA polymers in stabilize 100 % of the enzyme activity for at least four weeks.

Altogether, the concept shown in Figure 1 seems to be valid in the presented case. Besides activating the enzyme by a factor of 30, the POx-IDA serve as excellent stabilizers for the enzyme laccase.

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High Molecular Weight Thermoresponsive Copoly(2-oxazoline)s

LCST polymers for better understanding smart hydrogels

Montasser Hijazi, Martin Schmidt, Joerg C. Tiller

Smart hydrogel are materials that change their degree of swelling upon an external trigger and have great importance in microfluidic devices and drug delivery applications. They are often composed of LCST polymers, which are soluble at low temperatures and become insoluble above a certain cloud point temperature T_{cp}. The swelling/deswelling behaviour of hydrogels composed of these polymers is often not comparable with the behaviour of the free polymers in solution, because such polymers are investigated in low concentrations in almost all studies, which are not representative for a hydrogel. In order to shine some light in this important issue, we synthesized a series of high molecular weight LCST polymers based on copoly(2-oxazoline)s and investigated them in concentrations that come close to the conditions you find in a smart hydrogel.

A series of copolymers prepared by copolymerization of 2-ethyl-2-oxazoline (EtOx) with the respective heptyl (HepOx), butyl (BuOx), and isopropyl (iPrOx) derivatives, respectively. The polymers were prepared by living ring opening polymerization and the molecular weights were between 20 and 40 kg/mol. The resulting copolymers show greatly different dependencies of their T_{cp} on concentration.

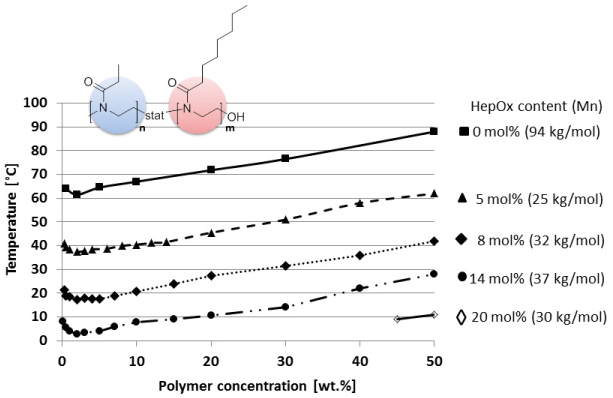

Figure 1: Cloud point temperatures T_{cp} of statistical copolymers of EtOx and HepOx in water in different concentrations.

As seen in Figure 1, the copolymerization of EtOx and HepOx leads to polymers, which exhibit decreasing LCSTs with higher HepOx content. The lowest T_{cp} (called LCST) typically occurs at a concentration of 2 -3 wt %. The copolymers with 8 mol% and 14 mol% HepOx, show an LCST far below room temperature at 9 °C and 3 °C, respectively. The copolymer with 20 mol% HepOx was only water soluble at concentrations above 40 wt%. Generally, increasing the polymer concentrations to higher values leads to greater T_{cp}s. Interestingly, the slope, which is nearly linear between LCST concentration and 50 wt% is similar for all polymer compositions, even for PEtOx.

The relatively slight variation of the comonomer side groups leads to very different phase diagrams (Figure 2). While P(EtOx-stat-HepOx)s all increase their T_{cp} with higher concentration, P(EtOx-stat-BuOx)s show much less strong dependence of T_{cp} on concentration with increasing BuOx content. In contrast, P(EtOx-stat-iPrOx) copolymers show two distinguished plateau regions for T_{cp} which becomes less pronounced with increasing iPrOx content.

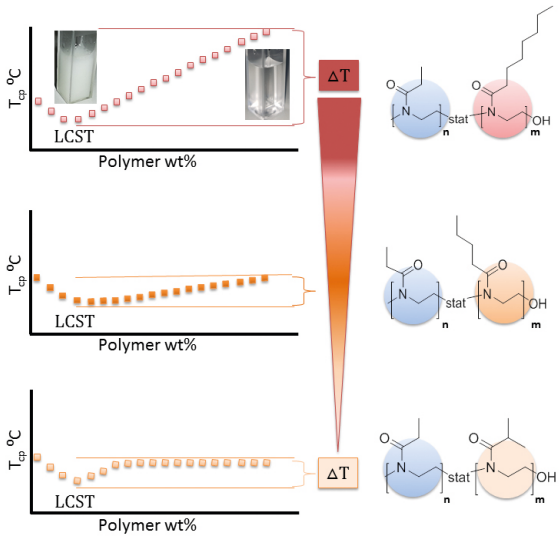

Figure 2: Comparison of phase diagrams of different copoly(2-oxazoline)s.

This shows that copolymerization of different 2-alkyl-2-oxazolines is not only a tool to control the LCST of the formed copolymers, but also to tune the respective phase diagram. It also indicates suited candidates for the possible synthesis of discretely thermoswitchable hydrogels. These properties might not only be used in POx-based networks and conetworks.

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Bioprocess Engineering (BPT)

A Combined Approach of Genome Mining and Activity Screening Revealed Novel Biocatalysts for Hydroxylation Reactions

Accessing novel biocatalysts for the oxidative functionalization of pharmaceutical compounds

Lisa Marie Schmitz, Katrin Rosenthal, Stephan Lütz

The selective oxyfunctionalization of nonactivated C-H bonds is still one of the most challenging reaction types in chemistry. Often expensive and complex catalysts and harsh reaction conditions are required, however the efficiency of many catalysts is lacking in terms of regio- and stereoselectivity. The oxygenation using cytochrome P450 monooxygenases (P450s) offers an alternative at ambient conditions. This group of enzymes catalyzes the reductive activation of molecular oxygen to transfer one atom onto the substrate leading to many chemical transformations of complex substrates. In order to find novel P450s for selective oxidations and with a new substrate scope, exploiting the natural diversity in microorganisms is a promising approach.

P450s in whole-cells are used in pharmaceutical and fine chemical industry to create new functional groups within biomolecules and to synthesize drug metabolites for pharmacokinetic and toxicity studies. To expand the P450 chemistry towards new reactions and new substrates the search in the natural P450 pool is a promising approach. Goal of this work was to identify so far underutilized P450 biocatalysts by a combined approach of genome mining and activity screening (Figure 1). The increasing number of whole genome sequencing projects reveals novel genes annotated to the P450 family on a daily basis. Therefore, a data-base analysis was performed to yield a list of microorganisms with a high total count of P450 sequences and high sequence diversity determined by the categorization into superfamilies and homologous families. To test functionality and activity of promising organisms from this list a screening in a microtiter plate format was performed. The strains were tested for the conversion of seven representative substrates. Several organisms with high reactivity and broad substrate acceptance without regard to size and properties were revealed.

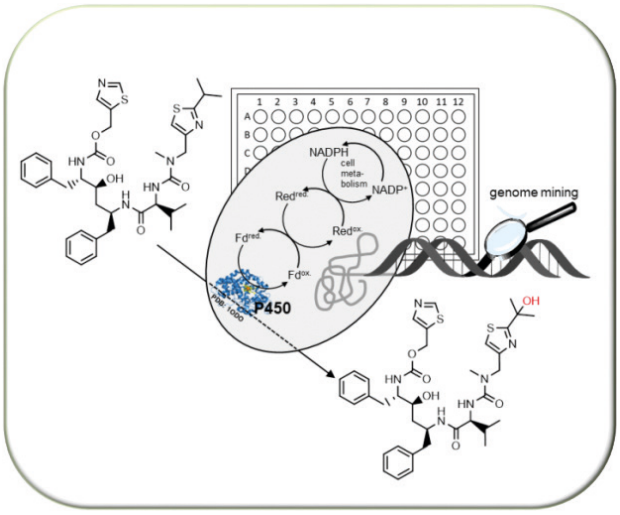

Figure 1: Schematic representation of a combined approach of genome mining and activity screening to receive promising whole-cell biocatalysts for hydroxylation reactions.

To further test the potential of the strain collection for the biotechnological application, the biotransformation of ritonavir with Actinosynnema mirum was transferred to a 1.7 L lab fermenter. A 90 % conversion could be reached after 48 h of fermentation (Figure 2). In total 13 different metabolites were formed which were isolated and further characterized by LCMS2 and NMR. Next to new oxidation products the three main ritonavir metabolites formed in human could be identified.

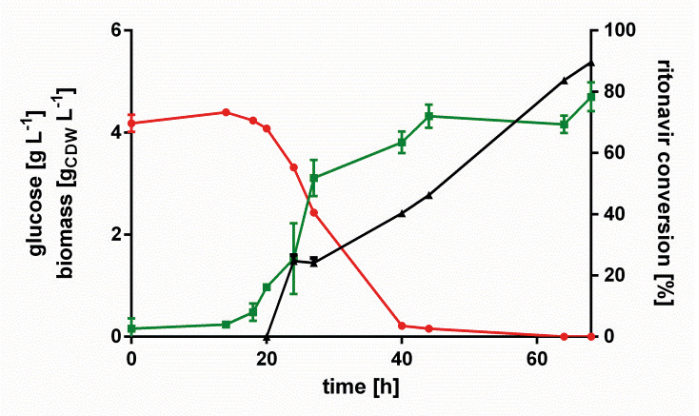

Figure 2: Biotransformation of ritonavir on preparative scale. The substrate ritonavir was added with a final concentration of 0.1 mg L^{-1} after 20 h of fermentation. Shown are biomass concentration (green), C-source consumption (red) and ritonavir conversion (black). Data points were calculated from duplicates.

The high product yields after scale-up confirm the potential of the described approach of genome mining and activity screening to receive strains with a great application opportunities in biotechnology and synthetic biology. Promising organisms can be used for a future preparative production of biomolecules.

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Process Dynamics and Operations (DYN)

Model Adaptation in Iterative Real-Time Optimization in the Presence of Model Uncertainties

Afaq Ahmad, Weihua Gao, Sebastian Engell

The term real-time optimization (RTO) denotes the optimization of the operating point or of the batch recipe of processing plants during the operation, based upon first principles models and targeting economic optimality. A key problem in any model-based optimization scheme is that the model usually does not represent the true behavior accurately, which is called plant-model mismatch. It can be handled using measurement information to correct the model. Two strategies are the adaptation of model parameters and the modification of the optimization problem by adding bias and gradient correction terms (called modifier adaptation, MA). However, it can happen that the corrected model does not satisfy the second order conditions of optimality at the true optimum of the plant which leads to oscillating behavior of the iterative optimization. This is called model inadequacy. In our approach, model adequacy is enforced in model parameter adaptation. By means of a simulation study of maximizing the product yield in a fed-batch reactor, we demonstrate that the proposed model adaptation procedure computes model parameters which make iterative RTO with MA converge faster and more reliably to the plant optimum.

RTO is a model based upper-level optimization system that is operated iteratively in closed loop and provides set-points to the lower-level control system in order to maintain the process operation as close as possible to the economic optimum.

The success of RTO depends on the quality of the model that is used in the optimization problem. The effort required for building and maintaining models often represents the bottleneck in the deployment of RTO solutions, and even sophisticated models cannot represent the real process exactly. Hence, an efficient RTO scheme typically uses both a rigorous plant model and data collected during plant operation to drive the plant to an optimal operation.

This article proposes to perform parameter estimation in order to improve the quality of the model in iterative RTO with MA. The new approach uses effective model adaptation (EMA) to ensure and to accelerate the convergence to the optimum in the presence of plant-model mismatch. The key idea is to update the model in the MA optimization only if the adapted model satisfies certain criteria of adequacy in order to guarantee local convergence.

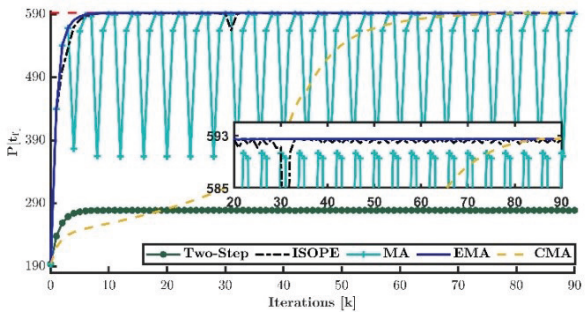

Figure 1: Comparison of iterative batch optimization schemes with respect to convergence of the plant cost using the two-step approach, ISOPE, MA, CMA and MA with EMA.

Figure 1 presents the performance of the new iterative RTO scheme and compares it with different RTO approaches that use model adaptation or a fixed model for trajectory optimization for a fed-batch reactor for penicillin production.

Due to the presence of structural mismatch, the two-step scheme where the model parameters are adapted based on the measurements converges to a set-point which is far away from the process optimum. The standard MA scheme initially moves quickly towards the optimal final penicillin concentration but then starts to oscillate because the model is inadequate near the plant optimum. The ISOPE scheme gives a better performance compared to the standard MA due to the model adaptation in each iteration. However, the cost near the plant optimum shows an oscillating behavior. The convex model approximation (CMA) scheme converges to the plant optimum as it handles the model adequacy issue. However, it can be observed that the rate of convergence to the process optimum is slow. In the MA with EMA algorithm, EMA finds adequate model parameter values that make the model adequate from the third iteration onwards and this ensures convergence to the true process optimum.

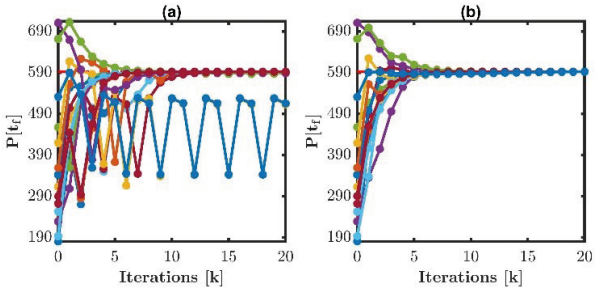

Figure 2: Evolution of the plant cost for different initial operating conditions. (a) MA with EMA, (b) MA with EMA-EA.

We enforce the model adequacy via slack variables in the objective of the parameter estimation problem to increase the performance of MA with EMA. To quantify the advantage of enforcing model adequacy, the simulation was run for different values of the initial operating conditions. Comparisons of both schemes, MA with EMA and with enforcing model adequacy (EMA-EA) are presented in Figure 2.

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An Accelerated Dual Method Based on Analytical Extrapolation for Distributed Quadratic Optimization of Large-Scale Production Complexes

Lukas Samuel Maxeiner, Sebastian Engell

Chemical production sites are significant consumers of energy and resources. These sites nowadays usually consist of plants that are operated by different companies. Therefore, improving the efficiency of the whole site by coordination between the different plants poses a challenging task. An approach to tackle this is distributed optimization using dual decomposition where all entities optimize their own objectives and only inform the coordinator about their consumption or production of shared resources for certain prices of those shared resources. The standard method to find the optimal prices are sub-gradient methods, which require many iterations. We have developed an accelerated method, which significantly speeds up the convergence by exploiting the structure of the dual function for quadratic problems. Two strategies for handling changing sets of active constraints were developed. It is shown that the performance of our algorithm is in most cases significantly better than that of other approaches.

In the process industries, the production plants in larger sites are interconnected by networks of raw and intermediate materials as well as energy carriers, as natural gas and steam at different pressure levels. In Figure 1, a schematic representation of such a site with n plants is shown.

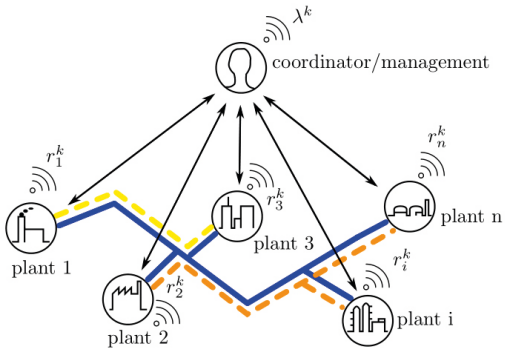

Figure 1: Schematic representation of a chemical site with networks for different resources. All plants communicate with a central coordinator, which iteratively determines the transfer prices for the shared resources.

A better coordination of the production and consumption of these shared resources provides a lever towards a more resource efficient production. However, site wide optimization poses a problem when different stakeholders (independent companies or business units within one company) need to share business-related information. Confidentiality reasons usually make the application of a monolithic approach to solve the site-wide optimization problem impossible.
Distributed solution methods can provide optimal production levels and distribution of resources while maintaining a large degree of confidentiality. Internal cost structures, plant models, constraints, and demand patterns do not have to be revealed. In this approach, the transfer prices for the shared resources are iteratively determined by a central coordinator based on the announced supplies and demands of the different plants for a given set of transfer prices. Therefore, the site becomes an internal micro-market. Once the optimal transfer prices have been found, the whole site produces optimally.
In the literature, there are various methods to solve distributed optimization problems. Many of them are based on sharing of more information than is possible in the setting here. Others require many iterations to converge to the optimum.
In our work, we developed a new method for the distributed optimization of coupled quadratic problems, which a variety of problems requires less iterations compared to other state of the art algorithms.

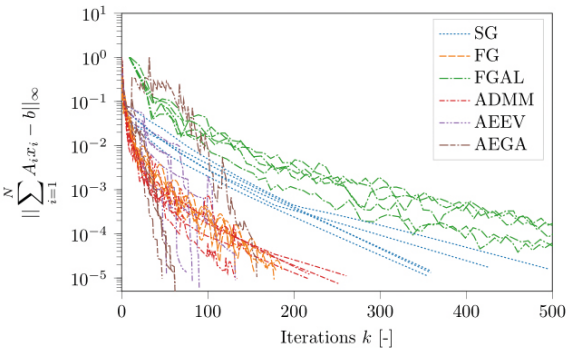

Figure 2: Evolution of the scaled imbalance for the sub-gradient method (SG), the fast gradient method (FG), the fast gradient adaptive Lipschitz approximation method (FGAL), alternating direction method of multipliers (ADMM) and the newly developed analytical extrapolation with extrapolation verification (AEEV) as well as analytical extrapolation with global approximation (AEGA).

This is demonstrated in Figure 2, where 10 plants that share 10 resources were coordinated. The reduction of the scaled imbalance between supply and demand for different methods over the number of iterations is shown. AEEV and AEGA are two different variants to handle the change of the active sets when the individual problems are locally constrained besides the global resource balance in the connecting networks.

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Modeling and Optimizing Control of Bioreactors

Lukas Hebing, Sebastian Engell

The performance of most bioprocesses in industry can be enhanced by using model-based optimization technologies as e.g. optimizing control. However, the main hurdles for applying these methods are the lack of predictive dynamic models of the complex processes, the lack of time to develop suitable models during the process design phase, and the resulting need for control with structural plant model mismatch. To overcome these obstacles, we propose a framework for modeling and optimizing control which allows us to build sufficiently accurate dynamic models within a short period of time and to use them for the optimizing control of key operating parameters. Plant model mismatch is compensated by the utilization of structurally different models in parallel which are adapted and evaluated online. Simulation studies showed that the process performance can be greatly enhanced with this method.

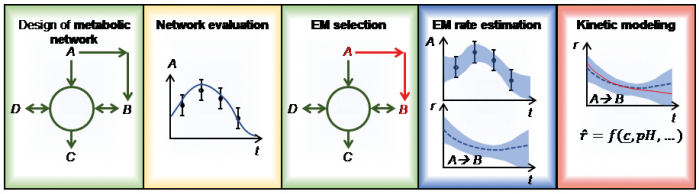

Figure 1: Overview of the modeling concept: First, a metabolic network of the production organism is designed and evaluated, then elementary modes (EM) from this network are selected as base reactions for the model. EM reaction rates are estimated and used for the selection and fitting of kinetic equations.

In the chemical and pharmaceutical industry, bioprocesses are used to produce very complex and valuable products as e.g. speciality chemicals or biopharmaceutics from simple raw materials by utilizing the metabolism of micro-organisms or cell cultures. Due to the complexity of these processes and the limited time for process development in the pharmaceutical industry, the operation of the processes is mostly kept simple and thus a high potential for optimization is ignored. The performance of biotechnological processes could be greatly enhanced by more advanced control methods based upon a mathematical representation of the process. When the response of the micro-organisms or cells to changes in process conditions can be predicted well enough, optimal trajectories of process inputs can be calculated. Applying optimizing control, these trajectories can be corrected during the process in order to optimally react to disturbances and process variability and to correct plant model mismatch.

The major hurdles for applying these methods are (1) the lack of suitable process models and the limited time to develop those and (2) the lack of algorithms for optimizing control which can cope with the characteristics of bioprocesses like infrequent measurements, non-linear behavior, a high variability, and structural plant model mismatch.

In a cooperation with the Bayer AG, we worked on solutions for these challenges and developed a framework for modeling and optimizing control.

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The models of the bioprocesses are built by combining knowledge-driven and data-driven elements. Whereas some aspects of bioprocesses are known sufficiently well (e.g. mixing and feeding, gas removal, basic metabolic reactions of the organism) others are completely unknown, e.g. the influences of process conditions on the meta-bolism. We take advantage of this knowledge and first identify a metabolic network of the organism and then a set of Elementary Modes (EM) which describe the metabolic turnover with a sufficient accuracy. Methods for the EM rate estimation were developed for the kinetic modeling of the influences of process conditions.

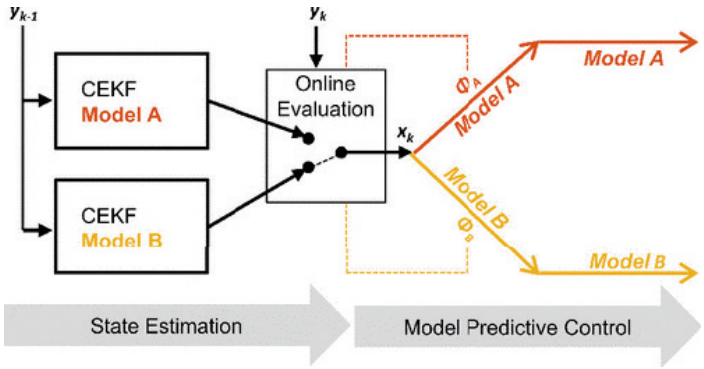

Figure 2: The concept for state estimation and model predictive control using multiple structurally different models. The prediction accuracy of each model is evaluated when new measurements are available. A model trust index Φ_i is calculated and used as a weight in the scenario-based multi-stage NMPC which calculates new optimal inputs for the process.

To further compensate for plant-model mismatch, we developed a process control strategy where multiple models are used in parallel (see Figure 2).

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Scheduling of a Consumer Goods Production Plant with Intermediate Buffer by Decomposition and Mixed-integer Linear Programming

Vassilios Yfantis, Christian Klanke, Francesc Corominas, Sebastian Engell

Varying demands and global competition pose significant challenges in the consumer goods industry. Exploiting market opportunities often leads to the need for an extension of the production capacities of manufacturing plants. This can be achieved by adding new plants or adding production units to existing plants which may require very significant investments. Another option is the reconfiguration of an existing plant layout to achieve higher throughputs at a relatively low cost. A potential reconfiguration strategy is the decoupling of production stages by buffers which increases flexibility and is efficient if the bottlenecks of the process vary over time. In this contribution, the scheduling of an industrial consumer goods production plant with two production stages with a buffer in between the stages is discussed. The solution can be used to assess the benefits of the modified layout and for the later online scheduling of the plant with the buffer. The scheduling algorithm is based on decomposition and mathematical programming. The generated schedules are compared to schedules for the current layout.

The layout of the plant that is considered here is shown in Figure 1. It consists of two sections, a formulation section and a packing section. Currently, the two sections are tightly coupled: each formulation unit feeds a packing line. In this layout, the total throughput of the coupled lines is the lower of the throughputs of both elements. As the bottleneck varies, there is a potential for better load distribution. Each packing line can only process certain products while each unit in the formulation stage can process every product. Also the total changeover time of a line is determined by the largest changeover time of the two stages, leading to unnecessary idle times. To overcome these limitations, the two stages can be decoupled by a buffer, as shown in Figure 1. In this flexible layout, the products can be transferred to any packing line that is capable of processing them and different production rates can be balanced by storage of unpacked products.

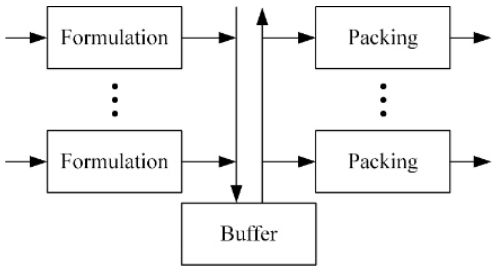

Figure 1: Schematic representation of the flexible layout.

The goal of the scheduling algorithm is to allocate different production orders to the production units, while accounting for constraints on the timing of the operations, changeover times, and the maximum capacity of the buffer. The problem was formulated as two mixed-integer linear programs, minimizing the changeover times and the completion time of the schedule. The first program provides an optimal packing stage schedule with emphasis on changeover time minimization. The second element schedules the formulation stage and tracks the buffer level, thus making the packing stage schedule feasible.

Due to its complexity and size, a rigorous solution of the complete optimization problem was not possible. For computational tractability, decomposition strategies for both subproblems were developed which schedule only a subset of the orders per iteration. The scheduling problem is then solved iteratively while accounting for the decisions made in the previous iterations. The scheduling algorithm was applied to several real demand scenarios and the results were compared to the schedules of the current layout, as provided by the planners at the plant. The solution time was <10 minutes.

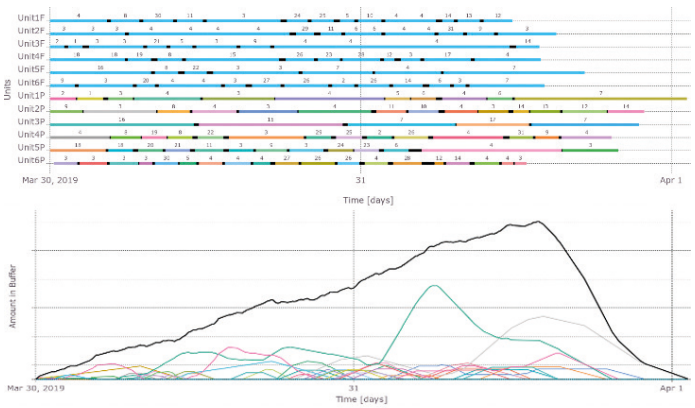

Figure 2: Resulting schedule of a real demand scenario, including 76 orders, 6 formulation units and 6 packing lines. In the bottom the resulting buffer profile is shown.

The results show that the algorithm can generate good schedules in short computation times. A clear benefit of the flexible layout over the current layout could be demonstrated.

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  8th International Symposium PSEASIA, Bangkok, Thailand, January 13-16, 2019

- S. Engell, S. Subramanian
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Solids Process Engineering (FSV)

3D-Simulation of Extrusion Process Parameters in Intermeshing Screw

Effective and cheap method for a detailed investigation of screw elements in twin screw extruders

Vanessa Düphans, Isabella Putz, Julius Arntzen, Markus Thommes

The hot melt extrusion in a co-rotating intermeshing twin screw extruder is an important manufacturing technique for pharmaceutical products. The modular screw design leads to an adjustable but complex process as a result of the combination of different unit operations. For a sufficient product quality, an understanding of the process as well as the prediction of process parameters in a specific screw element are of great importance. Based on these challenges, a new 3D simulation was performed in Ansys Fluent. This analysis of the screw elements of a twin screw extruder was possible with a low computational effort due to the implementation of a pulse transmission method.

A 3D-simulation in Ansys Fluent requires the knowledge of the complex flow types in a screw element (Figure 1). The Couette flow is caused by the screw rotation and the resulting shear strain of the material on the wall of the extruder and between the extruder screws. The Poiseuille flow is generated by a pressure gradient analogous to the pipe flow. But in contrast to a pipe, the Poiseuille flow in the extruder moves against the flow direction due to the back pressure in front of the die. Furthermore, a leakage flow occurs in the gap between the two screws and the screws and the extruder wall.

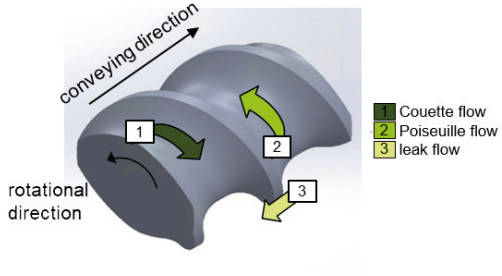

Figure 1: Schematic representation of different flow types in a screw element.

The simulation is set in four steps from starting with a simple flow tube to the complex twin screws (Figure 2). A stationary, laminar and isothermal flow with an incompressible Newtonian fluid is assumed. Normally a moving mesh is used for the screw rotation. However, in this case an apparent movement can be implemented. This procedure offers the advantage of a significantly shorter computing time of around twenty minutes on a regular desktop computer. For every individual geometry, the pressure difference at different mass flows was determined simulatively and analytically. Thus the results agreewell.

Figure 2: Simulation development from simple to complex geometries.

An analysis of the twin screw leads to detailed information about the element: The flow behavior, applied shear stress to the material, pressure difference (Figure 3), power characteristics and residence time distribution.

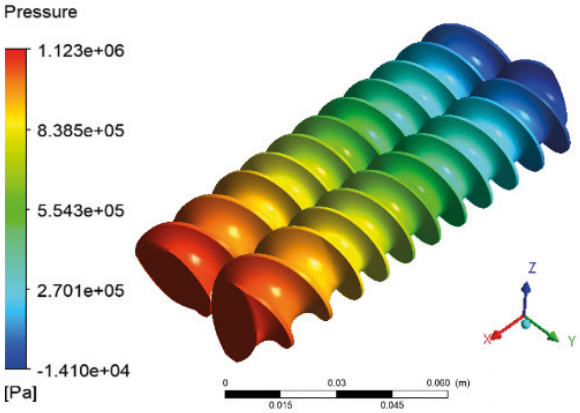

Figure 3: Pressure difference over the screw elements.

For a first validation silicon oils with different viscosities were used (Figure 4). The screw configuration consists of conveying elements with different pitches (20 and 30 mm). During the process the screw speed was varied. The pressure was measured at two positions in front of the die. The deviation at 100 rpm is caused by air bubbles that are produced at higher screw speeds, which decreases the viscosity and thus also the pressure difference in the extruder.

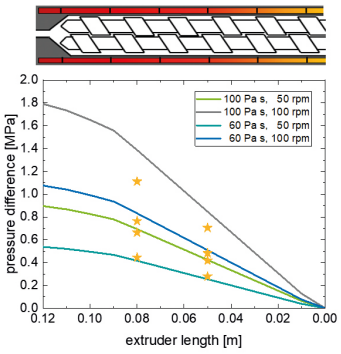

Figure 4: Pressure characteristics for the conveying element (simulation results (lines) and experimental values (stars)).

In conclusion the 3D-simulation was successfully performed. Important process parameters can be analyzed in detail for different types of screw elements with a lower computational effort.

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Preparation of Submicron Particles and Electrostatic Precipitation

A process to produce drug formulations with enhanced dissolution behavior

Anna Justen, Adrian Dobrowolski, Gerhard Schaldach, Helmut Wiggers, Markus Thommes

The low aqueous solubility of novel drug molecules is one of the main challenges in drug formulation these days. A common formulation concept to improve solubility, besides micronization, are solid dispersions. In solid dispersions the drug particles are embedded in a carrier matrix. Recently, spray drying has been suggested as manufacturing technique for submicron particles embedded in a solid matrix, although limited drug loads and low throughputs wereobtained.

In this study submicron drug particles were produced with ultrasonic atomization technique in a specially designed aerosol generator. An aerosol from a solution of an active pharmaceutical ingredient (API) and acetone was nebulized with ultrasonic frequency of 3 MHz. With this particularly high resonance frequency, it was possible to produce small droplets, which were dried in a drying operation. Submicron API particles resulted and were separated via electrostatic precipitation. A Melt Electrostatic Precipitator (MESP) was used to precipitate the submicron particles towards a molten carrier matrix of xylitol (Figure 1).

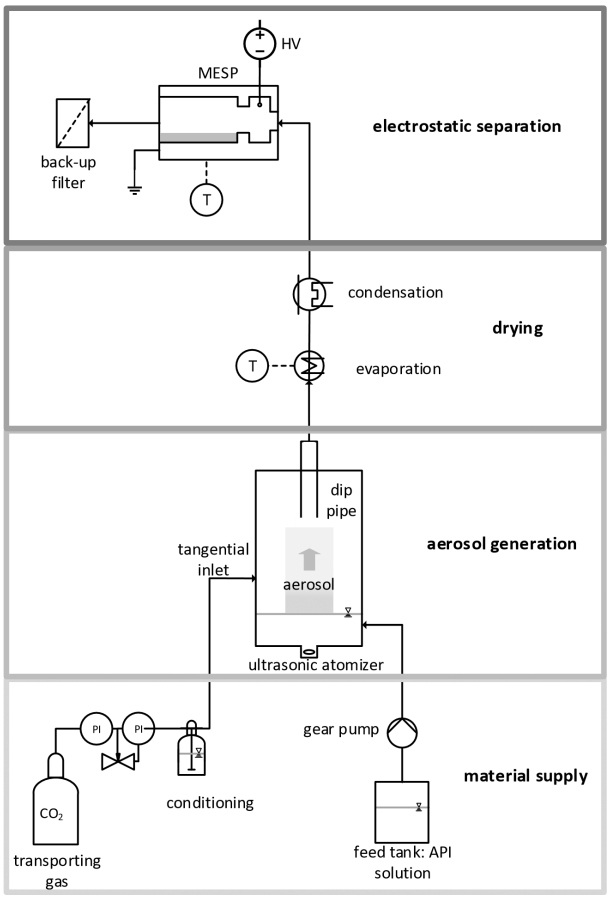

Figure 1: Experimental set-up.

Drug loads of the precipitated API in the xylitol melt were determined at different applied voltages. Voltages between the corona inception and the corona breakdown were chosen and experiments at a constant loading time were performed. With increasing applied voltage an increase of precipitated API was observed . At a loading time of 5 min drug loads of up to 0.25 wt.% could be obtained (Figure 2).

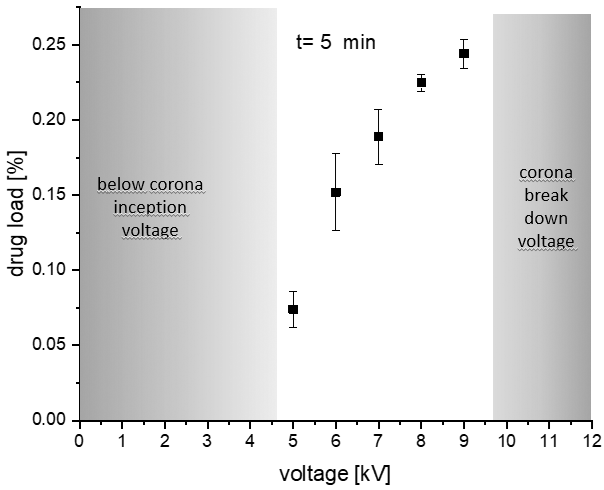

Figure 2: Drug load of phenytoin in a xylitol matrix at different voltages (av±s, n=3).

With the new developed aerosol generator the production of dry nanoparticles with a d50 of 300 nm and a high mass flow were achieved. It is a promising tool to generate submicron particles in laboratory scale and also has potential for scale-up trials. The combination of the aerosol generator and the MESP enables the production of drug containing matrices. As it could be shown in further studies a faster dissolution in water compared to pure drug particles was achieved.

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Influence of Residence Time in Manufacturing Amorphous Solid Dispersions via Hot Melt Extrusion

Tobias Gottschalk, Birte Grönniger, Tim Feuerbach, Friederike Wolbert, Gabriele Sadowski, Markus Thommes

The poor solubility of new drugs substance is amajor challenge in today's pharmaceutical research. Therefore, the formation of amorphous solid dispersions (ASDs) via hot melt extrusion (HME) is one promising approach. Within this formulation, the drug is molecularly dissolved in an amorphous carrier. The crucial parameter within this process is the dissolution of the drug in the carrier. Since the drug needs to be completely dissolved, the minimal required temperature, called solubility temperature (Ts), given by the phase diagram of the drug/polymer mixture, has to be considered beforehand. It is important to keep in mind, that the Tsgives information about the equilibrium state. Because of limited residence times (RTs) in HME it is questionable whether this state is reached under process conditions. Therefore, this work shall investigate the influence of the residence time on the dissolution of drug in the polymer.

In order to investigate the influences of RT and temperature on the formation of ASDs, extrusion experiments were carried out in a DSM xplore micro compounder, a laboratory scale extruder with around 5 ml of capacity. 3 g of formulation were fed into the extruder and a screw speed of 50 rpm was used. The RT of the material was adjusted by an outlet valve and was varied from 0.25, 1, 3 to 10 minutes. The process temperature was varied in a specific distance (ΔT) to T_s. Drug weight fractions from 0.2, 0.25 to 0.3 were used.

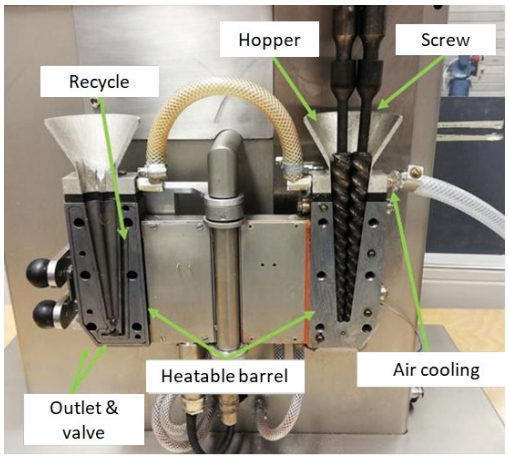

Figure 1: DSM Xplore micro compounder with recycle loop.

The resulting extrudate strands for the formulation of ITR/SOL/0.25 are depicted in Figure 2.

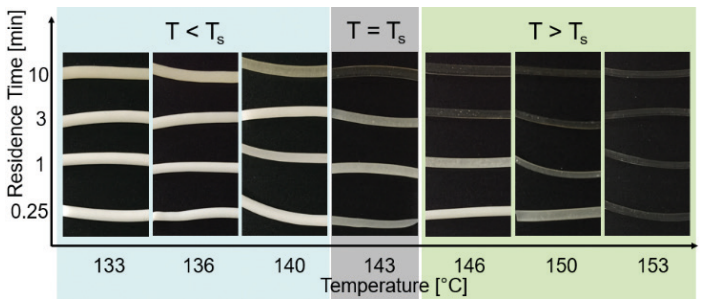

Figure 2: Extrudate strands for different RTs and material temperatures (ITR/SOL/0.25). (opaque = remaining crystals, transparent = completely dissolved drug).

It becomes obvious, that in all strands extruded below T_s crystals are remaining, independent of material temperature or RT. This experimental results are in agreement with the statement of the phase diagram. Comparing the extrudate strands on the solubility line, the effect of the RT becomes clear. While the extrudate strands with RTs equal or below 3 minutes still remain opaque, the strand after 10 minutes is transparent. This shows that the predicted solubility of the phase diagram is not reached fast. It even lasts for more than 3 minutes to reach equilibrium stated by the phase diagram. The same effect can be seen at temperatures above T_s. Since the driving force is enhanced by the higher temperature difference to the T_s, the drug dissolves faster. Therewith, the hypothesis, the RT influences the formation of ASDs, is valid. Another important aspect is the range of RTs. In production scale extrusion, RTs are around 30 seconds until 3 – 4 minutes. The results of this work show, that in this common RT range, the dissolution of drug might already by restricted by an insufficient RT.

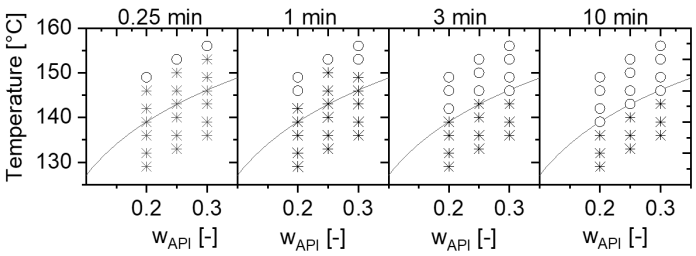

Figure 3: Dissolved drug (○) or remaining crystals (*) depending on different RTs and material temperatures.

The finale summary of the experiments is depicted in the phase diagrams for different RTs (Figure 3). It can be seen that the described results for a drug weight fraction of 0.25 are similar to the results for other weight fractions. The predicted phase diagrams were reached after 10 minutes.

In summary, it was shown, that an insufficient residence time can lead to an incomplete dissolution of the drug. If a sufficient residence time was provided, the predicted phase diagrams were found experimentally.

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Technical Biochemistry (TB)

Cannabinoid synthases and osmoprotective metabolites accumulate in the exudates of *Cannabis sativa* L. glandular trichomes

Paweł Rodziewicz, Stefan Loroch, Łukasz Marczak, Albert Sickmann, Oliver Kayser

Cannabinoids are terpenophenolic compounds produced by Cannabis sativa *L., which accumulate in storage cavities of glandular trichomes as a part of the exudates. We investigated if tetrahydrocannabinolic acid synthase and cannabidiolic acid synthase, which are involved in the last step of cannabinoid biosynthesis, are also secreted into Cannabis trichome exudates. The exudates were collected by microsuction from storage cavities of Cannabis glandular trichomes and were subjected for proteomic and metabolomic analyses. The catalytic activity of the exudates was documented by cannabigerolic acid biotransformation studies under hydrophobic conditions. Electrophoretic separations revealed protein bands at ~ 65 kDa, which were further identified as tetrahydrocannabinolic acid synthase and cannabidiolic acid synthase. The accumulation of the enzymes in trichome exudates increased substantially during the flowering period in the drug-type Cannabis plants. The content of cannabinoids increased significantly after incubating hexane-diluted trichome exudates with cannabigerolic acid. In this study, we showed that Cannabis glandular trichomes secrete and accumulate cannabinoid synthases in storage cavities, and the enzymes able to convert cannabigerolic acid under hydrophobic trichome-mimicking conditions. Metabolite profiling of the exudates revealed compounds with hydrophilic, osmoprotective and amphiphilic properties, which may play a role in providing a necessary aqueous microenvironment, which enables enzyme solubility and biocatalysis under hydrophobic conditions of glandular trichomes.*

In this study we identified THCAS and CBDAS in the exudates of Cannabis glandular trichomes, which accumulate during the flowering period, and remain catalytically active under hydrophobic conditions. Since these enzymes do not exhibit unusual properties for being solubilized under hydrophobic conditions, the compounds with hydrophilic and amphiphilic properties detected in the exudates may play a role in creating an aqueous microenvironment necessary for biocatalysis. More studies are needed to identify the exact role of the secreted compounds in trichome metabolism, the location of cannabinoid synthases within the ultrastructural network of Cannabis exudates (Figure 1), the contribution of the secreted synthases to the overall production of cannabinoids, and also the nature of metabolite transport in glandular trichomes. More investigations should also concern structural changes cannabinoid synthases undergo during secretory pathway, and especially the significance of the post-translational modifications on the structure, activity and solubility of these enzymes. Further studies should also include analysis of trichome exudates from other plant species, which may result in identification of other secreted enzymes (Figure 2). Understanding the mechanisms of the biocatalysis in glandular trichomes will contribute to the development of these secretory structures as natural biosynthetic factories, and may also advance the field of biosynthesis of secondary metabolites in organic solvents.

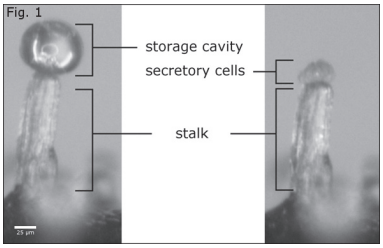

Figure 1: Capitate-stalked glandular trichome at 7th week of the flowering stage from the drug-type Cannabis (Euphoria) strain before (left) and after microsuction of the exudates (right). The applied technique enabled precise sampling of the exudates from storage cavities without disrupting the secretory cells.

Cannabinoid synthases exhibit similarities to other berberine bridge-like enzymes in terms of sequence and physicochemical propertie. Also, the structural characteristics of THCAS are rather typical for the enzymes soluble in aqueous buffers with polar amino acids exposed on the surface of the protein. For example, both cannabinoid synthases share 47% sequence identity (65% similarity including substitutions) with nectarin V secreted into the floral nectar of tobacco. Apart from playing a role in attracting pollinators, these metabolites also constitute a working environment for the enzymes catalyzing *ex vivo*. Osmoprotective compounds, such as sugars, polyols, and polar amino acids, are able to maintain the essential configuration of the enzymes by providing the hydration shell, especially in conditions with limited water activity.

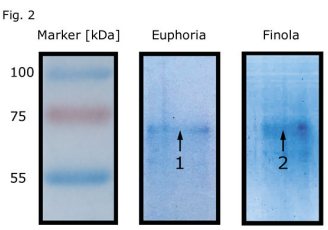

Figure 2: Coomassie-stained electrophoretic separations of proteins extracted from the exudates collected from 800 glandular trichome storage cavities from Euphoria and Finola Cannabis plants. Protein bands indicated with numbers were identified as THCAS (1) and CBDAS (2).

Osmolytes and amphiphiles were also found in the glandular secretions of coltsfoot (*Tussilago farfara* L.), but the extract was not tested for the presence of proteins. However, in case of other aromatic plants, such as thyme, sage, and rosemary, in addition to carbohydrates, the secreted proteinaceous component was also detected, but not yet identified. In turn, in glandular trichomes of *Solanum* species, which also produce large amounts of osmolytes and amphiphilic compounds, polyphenol oxidase was found to be the main secreted enzymatic component. Likewise, cannabis exudates also constitute a mixture of proteins and metabolites with hydrophobic, amphiphilic, and hydrophilic properties. The histochemical analysis of the storage cavities of glandular trichomes of Cannabis, but also hops and *Leonotis leonurus* L., revealed ultrastructural system of microchannels and secretory vesicles. Although, its role in trichome metabolism as well as the exact components were not precisely determined, it was found that the dense layer delimiting secretory vesicles comprise of pectin polysaccharides, and constitute an interface between hydrophilic and lipophilic regions, which further suggest emulsion properties of the exudates.

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Technical Biology (TBL)

Combinatorial Biosynthesis of Lipoxygenase Inhibitors in a Genetically Engineered *Myxococcus xanthus* Strain

Harnessing chemical space to improve bioactivity

Angela Sester, Lea Winand, Markus Nett

The natural products myxochelin A and B are potent inhibitors of the enzyme human 5-lipoxygenase which is involved in inflammatory diseases such as asthma as well as cancer development. Previously we showed that the myxochelin biosynthetic pathway in Myxococcus xanthus *can be genetically engineered to yield the imidazoline featuring derivative pseudochelin A. In this study, we have pursued a feeding strategy in order to introduce artificial building blocks into the biosynthetic pathway. This approach has led to the production of a number of myxochelin derivatives with improved bioactivity.*

The soil-borne myxobacterium *Myxococcus xanthus* is known as a producer of siderophores named myxochelins (Figure 1). In a screening programme myxochelin A was found to suppress the growth of leukemia cells and subsequent pharmacological characterization revealed human 5-lipoxygenase as the molecular target. Due to its potent bioactivity, which is comparable to the FDA-approved drug zileuton, myxochelin A has become a promising lead structure for the development of new anticancer drugs. Moreover, there is a strong interest in the generation of myxochelin derivatives for the investigation of structure-activity relationships.

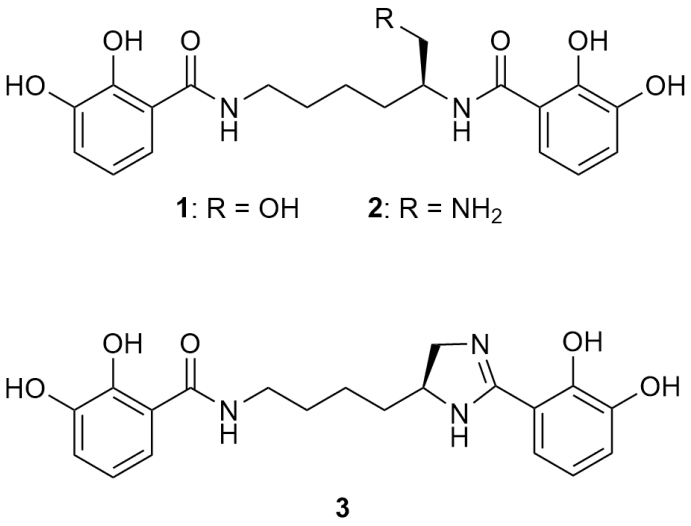

Figure 1: Chemical structures of myxochelin A (1) and B (2) as well as pseudochelin A (3).

In this study, we exploited the substrate promiscuity of the myxochelin pathway enzymes. For this, the previously engineered, pseudochelin-producing *M. xanthus* strain was fed with analogues of 2,3-dihydroxybenzoic acid (DHBA), which serves as a biosynthetic precursor. Due to the random incorporation of the DHBA surrogates at two possible positions, up to nine non-natural derivatives could be obtained after a single feeding experiment, though in very different yields. Upscaling of the fermentation volume and the development of a chromatographic separation process enabled the production of 10 derivatives in large quantities (Figure 2).

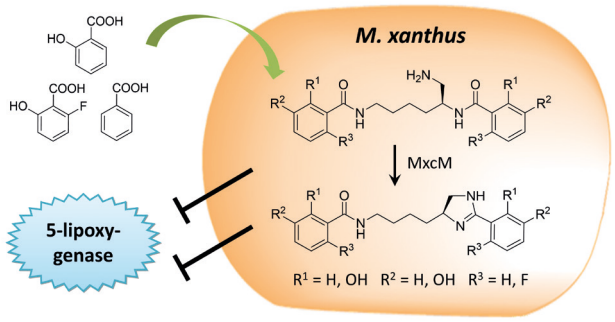

Figure 2: Generation of myxochelin and pseudochelin derivatives in a genetically engineered *M. xanthus* strain.

Eventually, these compounds were tested for their inhibitory activity against human 5-lipoxygenase. The measured IC_{50} values were rated against those of myxochelin A. This analysis revealed for the first time that myxochelin B and pseudochelin A possess superior bioactivity in comparison to myxochelin A. Furthermore, some unnatural pseudochelin derivatives are more potent 5-lipoxygenase inhibitors than myxochelin B. Altogether a set of potential new drug candidates were created and identified in this study.

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A. Sester, L. Winand, S. Pace, W. Hiller, O. Werz, M. Nett, J Nat Prod, 82, 2544-2549 (2019).

Massiliachelin, an antibiotic from *Massilia* sp. NR 4-1

Diatoms induce siderophore biosynthesis in *Cupriavidus necator*

Jan Diettrich, Hirokazu Kage, Markus Nett

In the past decades the number of multidrug-resistant organisms has dramatically increased. In combination with treatment failures these organisms have become a considerable threat to public health worldwide. The emergence of resistance to antimicrobial compounds is even more threatening considering that the number of newly approved drugs per year is continuously decreasing. The majority of antibiotics, which are now in clinical use, were originally discovered from Gram-positive bacteria. In recent years, however, Gram-negative bacteria have attracted increasing attention as producers of antimicrobial metabolites.

Massilia sp. 4-1 is a Gram-negative, aerobic, non-spore forming rod-shaped β-proteobacterium which is known to produce the antibiotic agent violacein. According to the OSMAC concept (one strain-many compounds) microbial strains often have the potential to produce a variety of secondary metabolites under different cultivation conditions. Using a genome mining approach, we identified a total of 16 biosynthesis gene clusters in *Massilia* sp. NR 4-1, illustrating the metabolic proficiency of this strain.

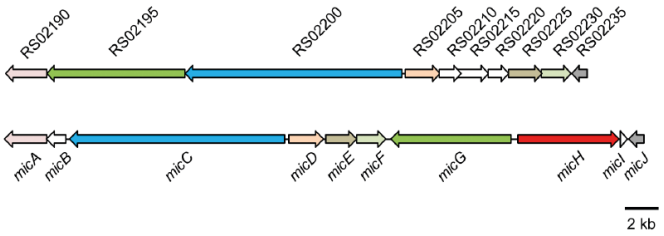

Figure 1: Organization of the massiliachelin gene cluster from *Massilia* sp. NR 4-1 (top) and of the micacocidin (mic) gene cluster from *R. solanacearum* GMI1000 (bottom).

One of these gene clusters showed notable similarities to a locus from the plant pathogenic bacterium *Ralstonia solanacearum* GMI1000 that is known to produce the antibiotic micacocidin (Figure 1). A closer inspection of the *Massilia* locus revealed the absence of a nonribosomal peptide synthetase gene responsible for the assembly of a thiazoline ring through condensation of a cysteine residue and subsequent cyclization. In order to track the predicted compound, we analyzed the metabolic profiles of *Massilia* cultures grown under different fermentation conditions. In this way, we discovered a compound, which was predominantly produced under iron deficiency. Its structure was elucidated on the basis of extensive spectroscopic analyses, including mass spectrometry as well as 1D and 2D NMR measurements. Bioinformatics was used to assign the absolute stereochemistry (Figure 2).

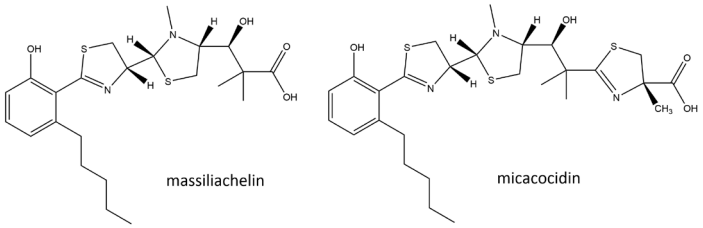

Figure 2: Chemical structures of massiliachelin and micacocidin.

The structure of this compound, which was named massiliachelin, was consistent with the architecture of the micacocidin-type assembly line. The predicted absence of the thiazoline ring structure could be confirmed. In summary, this study is an illustrative example of the genome mining approach where genomic data is analyzed, a promising compound is predicted and finally isolated and elucidated.

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Industrial Chemistry (TC)

Improving Aqueous Biphasic Hydroformylation of Unsaturated Oleochemicals

Jonas Bianga, Norman Herrmann, Tim Riemer, Thomas Seidensticker, Dieter Vogt

The production of aldehydes by hydroformylation of alkenes is highly relevant for the chemical industry, since these can undergo numerous subsequent reactions to form for instance alcohols, amines, and carboxylic acids. Generally, aldehydes from oleochemicals can serve as platform chemicals for gaining access to bifunctional molecules, which are interesting as polymer precursors. Performing hydroformylation with a water-based solvent system enables efficient product separation from the aqueous catalyst phase for the realization of more sustainable processes.

Homogeneous catalysts possess a huge potential for functionalizing unsaturated oleochemicals, such as unsaturated fatty acids and derivatives thereof. As presented in Figure 1, aldehydes are accessible by Rh-catalysed hydroformylation, which can undergo numerous subsequent reactions, to carboxylic acids, alcohols or amines. Bifunctional molecules are thus formed potentially having very interesting applications as precursors for polycondensates, lubricants or surfactants.

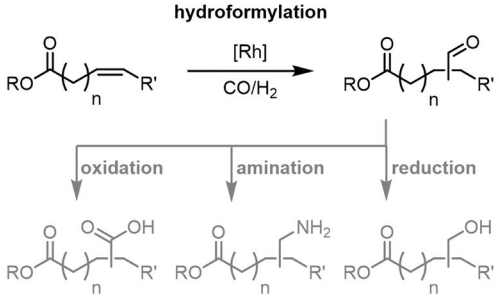

Figure 1: General scheme of hydroformylation.

The goal of the first step was to improve the productivity of aqueous biphasic hydroformylation of unsaturated oleochemicals.

To improve the reaction rate the miscibility of water and the fatty compound was increased by addition of the green solvent 1-butanol as co-solvent. For the first time, the concentration of solvents, substrate and product within the reaction progress were experimentally examined in a biphasic system under 20 bar pressure of synthesis gas and 140 °C and are presented in a tetrahedron diagram (Figure 2).

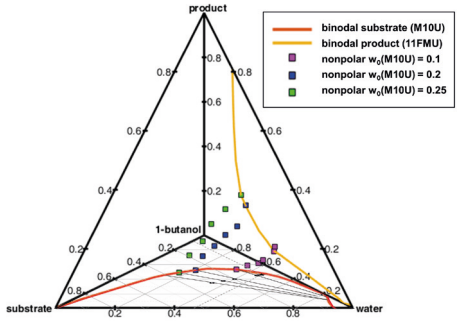

Figure 2: Detailed phase investigation for reaction progress in aqueous biphasic reaction system under reaction conditions.

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A new system for the phase investigation has been developed to do so. By the help of this investigation it was possible to increase the efficiency of the reaction process reported so far. With simultaneously high reaction rates (TOF = >5,000 h^{-1}), the space-time yield of the reaction reached values of > 120 g l^{-1} h^{-1} and could be improved significantly without negatively affecting catalyst leaching. Thus, the overall productivity of the aqueous biphasic hydroformylation of the castor oil derived methyl 10-undecenoate has been increased. In a second step it was possible to reduce the loading of the co-solvent 1-butanol using a jet-loop reactor. For the first time significant yields (>40 % after 1 h) were obtained in the absence of any co-solvent, which is very beneficial, since aldehyde products and substrate form a pure product phase enabling straightforward separation.

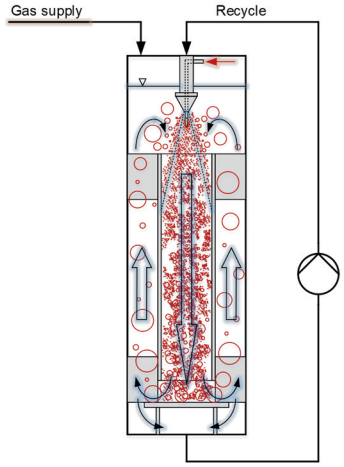

Figure 3: Scheme of a jet-loop reactor for the conversion of oleo chemicals under aqueous biphasic conditions.

The Jet-Loop Reactor (Figure 3) identifies itself as a very efficient tool for the conversion of oleo chemicals under aqueous biphasic conditions as demonstrated by hydroformylation. Compared to conventional stirred tank reactors, the Jet-Loop Reactor enables a significant decrease in co-solvent loading and a significant increase in substrate loading to improve overall reaction performance by intensified gas-liquid-liquid mixing.

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Selectivity control in homogeneously catalyzed carboxytelomerisation of 1,3-butadiene with several alcohols

Widening of substrate scope and investigations on functional group tolerance

Dennis Vogelsang, Johanna Vondran, Kevin Hares, Kevin Schäfer, Thomas Seidensticker, Andreas J. Vorholt

In terms of sustainable chemistry, highly atom efficient reactions, where all the applied substrates appear in the desired product, and energy-saving, selective reaction routes are of need. A helpful tool to establish high selectivity under mild reaction conditions is homogeneous catalysis. A representative homogeneously catalyzed atom efficient reaction is the carboxytelomerisation, the formal dimerization of 1,3-dienes under attack of an alcohol nucleophile in the presence of carbon monoxide forming unsaturated carboxylic acid derivatives. The feasible mono-, di- and polyesters open a wide range of applications in surfactants, lubricants, plasticizers, synthetic fats and pharmaceuticals. In this work, we show ways to control selectivity and investigate influences of several alcohols in terms of carbon chain length, steric hindrance, presence of aromatic groups and electron donating groups to overcome limitations and widen the range of novel C9-acid esters.

Homogeneously catalyzed carbonylation reactions are of great interest in academia and industry for gaining access to a broad variety of carboxylic acid derivatives. Principally, high catalyst activities and excellent selectivities can be reached due to the defined catalyst structure, contributing to highly atom economic reactions, as e.g. manifested for Pd-catalyzed carbonylation reactions like carboxytelomerisation.

Previously, carboxytelomerisation was established for the conversion of 1,3-butadiene, ethanol and carbon monoxide to the linear unsaturated C9-pelargonic ethyl ester. These C9-pelargonic acid derivatives are of high economic interest and already used in versatile industrial applications as in herbicides, lubricants or spreading agents as well as cosmetics. Commonly, pelargonic acid is produced on industrial scale through the ozonolysis of oleic acid or erucic acid. As a disadvantage, ozonolysis is harmful and its production is highly energy demanding. The atom efficient carboxytelomerisation represents a competitive alternative to obtain the unsaturated C9-acid derivatives from basic chemical resources in excellent selectivities.

In here, an application of several alcohol substrates is subject of research in terms of carboxytelomerisation to widen the range of novel C9-acid esters.

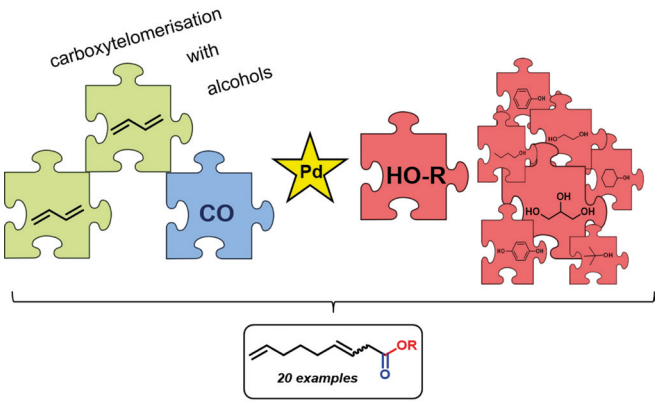

Figure 1: Substrate scope in carboxytelomerisation of butadiene.

Substrates with a lower nucleophilicity like phenol, or sterically demanding groups such as in *tert*-butyl alcohol exhibit a lower activity in carboxytelomerisation. Nevertheless, formation of the desired unsaturated C9-acid is facilitated by extended reaction time in these cases. In addition to simple monoalcohols, we found more complex molecules like vanillin and ascorbic acid to be active in the carboxytelomerisation with 1,3-butadiene and CO resulting in moderate yields, whereby electron donating functional groups are tolerated. Additionally, we were able to shift selectivity towards mono-, di- or polyester formation in case of polyalcohol substrates through the number of applied 1,3-butadiene equivalents. Finally, the reaction sequence including relative reaction rates of formation of mono-, di- and polyesters is estimated using the example of glycerol. Reactivity of primary alcohol groups is higher than reactivity of secondary alcohol groups, and reactivity of secondary alcohol groups is higher than reactivity of tertiary alcohol groups, shown in Figure 2.

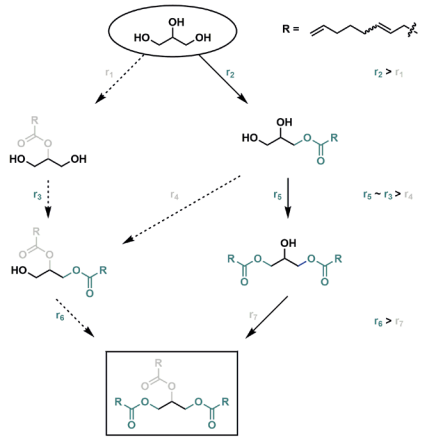

Figure 2: Reaction sequence of the carboxytelomerisation of 1,3-butadiene with glycerol.

Consequently, a highly controllable, comprehensive synthesis method for medium-chain C9 mono-, di- and triglycerides is developed resulting in a variety of industrially attractive products.

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Aqueous Biphasic Hydroformylation of Methyl Oleate

A green solvent-only strategy for homogeneous catalyst recycling

Norman Herrmann, Jonas Bianga, Tom Gaide, Marisa Drewing, Dieter Vogt, Thomas Seidensticker

The production of aldehydes by means of renewable resources is of high relevance for the chemical industry, as these can also undergo numerous secondary reactions to instance alcohols, carboxylic acids, etc. An alternative strategy for the Rh-catalysed hydroformylation of technical-grade methyl oleate in aqueous-media has been developed. This is achieved with the water-soluble Rh/NaTPPTS catalyst dissolved in a green polar phase consisting only of the safe and benign solvents water and 2-propanol. Along with efficient immobilization and recycling of the catalyst, excellent chemo- (> 96%) and regioselectivity (> 98%) to the desired branched aldehyde products is achieved. Beneficially, a pure nonpolar aldehyde product phase is obtained after reaction, containing only low amounts of 2-propanol (< 2%) and keeping catalyst leaching very low (< 0.5%). The catalyst phase is reused in up to 10 recycling runs, reaching accumulated turnover numbers of up to 20,000.

Several findings in our continuous endeavour to develop sustainable processes for the homogeneously catalysed conversion of renewables combined with efficient catalyst recycling strategies led us to revisit the hydroformylation of methyl oleate **1**. The goal was to develop a simple and efficient access to the much desired and highly interesting internal aldehydes **2**. In order to enable catalyst recycling, the proven strength of water for catalyst immobilisation was to be used, leading to the choice of the catalyst system for the already established Rh/NaTPPTS. In addition, technical grade methyl oleate from transesterification of high oleic sunflower oil was to be used to demonstrate feasibility for potential industrial applications. Furthermore, the aim was to obtain a pure product phase at the end of the reaction with minimal cross solubility of the used solvents and thus a low catalyst leaching.

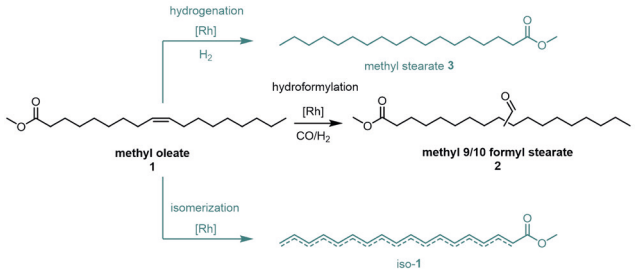

Figure 1: Hydroformylation of methyl oleate (1) to methyl 9/10-formyl stearate (2) and typical by-products.

For the selected ^{i}PrOH/H_2O system, the reaction parameters are optimized towards high chemoselectivity and catalyst productivity. As expected, high temperatures (140°C) as well as catalyst concentration and pressure favour the formation of the desired aldehydes. We limited the catalyst concentration to 2.5 mol% and pressure to 50 bar and examined the Rh/P ratio, which was optimal at 1/10. After a reaction time of one hour, about 60% of the desired branched aldehydes **2** are already formed. During the entire reaction time, only a maximum of 2% hydrogenation product is produced. The reaction reaches completion (conversion of methyl oleate >99%) after approx 12 hours reaction time with almost quantitative yield of the desired aldehyde products (98 %). After the reaction parameters have been investigated, the phase distribution of the critical components must be considered. In any experiment using 2-propanol, the product forms a clear, single organic phase upon the aqueous catalyst phase and can easily be decanted (Figure 2).

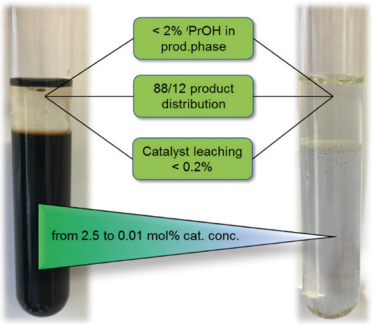

Figure 2: Photograph of the reaction mixtures after aqueous biphasic hydroformylation of methyl oleate (1) with full conversion at a catalyst concentration of 2.5 mol% (left) and at decreased catalyst loading of 0.01 mol%.

Recycling of the aqueous catalyst phase showed that the catalyst/ligand system remains stable for ten recycling cycles and exhibits lowest catalyst leaching of max. 2% in total. Further recycling runs with a reduction of the catalyst concentration of 0.5 and 0.01 mol% show 10 and 6 recycling runs, respectively with a total turnover up to 20,000 (Figure 3).

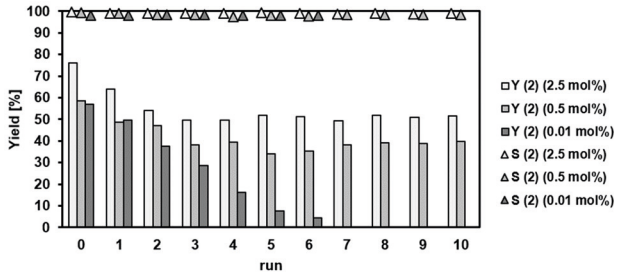

Figure 3: Yield (Y) and selectivity (S) of the product methyl (9/10) formyl stearate (2) in the catalyst recycling experiments at 2.5 mol% (light-grey), 0.5 mol% (mid-grey) and 0.01 mol% (dark-grey).

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Process Development for the Rh-Catalyzed Reductive Amination in a Thermomorphic Multiphase System

Kai U. Künnemann, Jonas Bianga, Ricarda Scheel, Thomas Seidensticker, Jens M. Dreimann, Dieter Vogt

For the first time the successful application of the homogeneously catalyzed reductive amination in a thermomorphic multiphase system (TMS) and the first reported scale-up of this reaction into a continuous process in a miniplant, which recovers and recycles the homogeneous catalyst in flow is presented. Herein, the model substrate 1-decanal reacts with the secondary amine diethylamine to the corresponding product N,N-diethyldecylamine. A thermomorphic multiphase system (TMS) is established as recycling strategy to recover and reuse the catalyst for the continuous process. After screening different solvents for the TMS and optimizing the reaction conditions in batch mode, the recycling of the rhodium catalyst was realized in a fully automated miniplant. Parameters influencing the stability of the process were identified and optimized to develop the continuous process. The process was operated in steady state over 90 h with yields >90 % of the desired product and low catalyst leaching <1 %/h.

Herein, we demonstrate the process development and first time implementation of the Rh-catalyzed reductive amination of 1-decanal in a TMS. Following six defined crucial steps of process development, we start with small scale experiments in batch all the way up to experiments in a continuous process. Important parameters for successful operation of the reductive amination like phase separation time, pressure, temperature and substrate concentration are determined in laboratory experiments using 25 ml batch autoclaves. For a scale-up the most promising conditions are applied in a 300 ml batch autoclave, to identify concentration profiles of the reaction and to set the desired residence time in subsequent CSTR operation (Figure 1).

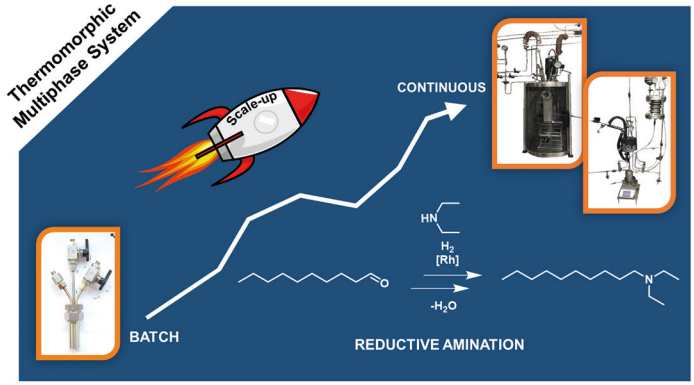

Figure 1: Schematic representation of scale-up concept of the reductive amination.

Having all these data compiled by a minimal amount of experiments in batch operation, the reaction is operated continuously in a reactor-separator miniplant process. With this, TMS can be applied to new reactions in continuous operation with minimal amount of experimental data combined with literature knowledge.

First the influence of the residence time was investigated (Figure 2). By looking at the product **3** yield at a constant pressure of 30 bar and 100 °C, a residence time of 1 h shows the same yield of 68 %, as at a residence time of 2 h (section 2). Therefore, the residence time of 1 h was chosen to further investigate the influence of the pressure. By lowering the pressure to 25 and 20 bar (section 4 and 5) the yield of product amine **3** decreases slightly from 68 % to about 60 %. No change in enamine **2** or aldolcondensate **5** yield was visible, only a slight increase at 20 bar (section 4) in the alcohol 4 yield of 3 % occurred. The stepwise increase of the pressure to 35 and 40 bar, respectively (section 6 and 7), increased the yield of the product amine **3** significantly, leading to yields up to 93 %, simultaneously diminishing the amount of unconverted enamine and aldol products. The average leaching in the long-term experiments of P and Rh is 4 ppm and 1 ppm, respectively, which both correspond to an average loss of <1 %/h based on the total quantity used in the process.

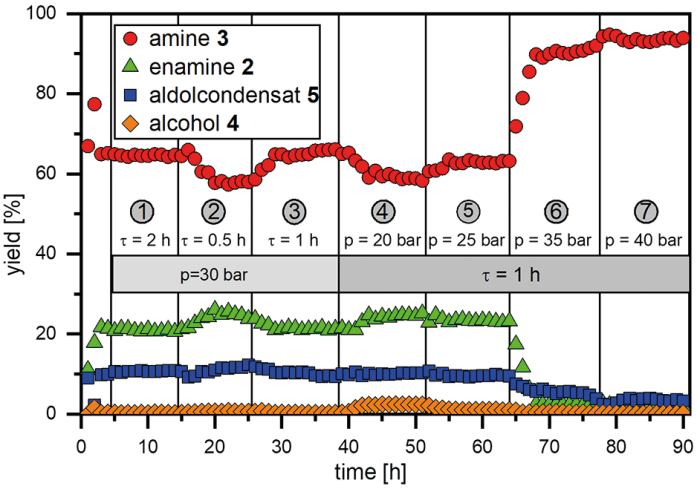

Figure 2: Sensitivity analysis for the reductive amination in a continuous miniplant process.

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Thermodynamics (TH)

Predicting Phase Equilibria for Sulfolane-Supported Selective Sour-Gas Absorption

The model ePC-SAFT was used to predict the vapor-liquid equilibria in aqueous amine solutions

Mark Bülow, Christoph Held, Gabriele Sadowski

In the chemical industry, aqueous amine solutions are widely used in sour-gas absorbers to reduce the emission of climate wrecking gases like CO_2. The effectivity of these amine solutions is enhanced by adding physical solvents. Predicting the absorption is challenging, involving multicomponent electrolyte systems, mutually affecting phase and reaction equilibria at wide temperature and pressure range. The thermodynamic model ePC-SAFT was used here to predict the selective absorption of CO_2 over H_2S (and vice versa) in an ultimately complex solution. The absorption depends on loadings of the sour gases and on the composition of the aqueous solution, which contains a chemical solvent (methyl diethanol amine (MDEA)) and a physical solvent (sulfolane).

Nowadays, industry aims at optimized absorption processes by reducing climate-wrecking gases in order to move towards a CO_2 neutral and environmentally benign chemistry. Aqueous amine solutions are typically applied to purify flue gas and natural gas in the oil&gas industry by absorption. This especially concerns the removal of sour gases like CO_2 and H_2S. To cover wider absorption ranges, including selective gas removal capabilities, the established aqueous solutions contain blends of different amines. On top, physical solvents are added to further expand the absorption range and the absorption kinetics to reduce the dimensions of the absorption columns. The design of efficient blends of amines and physical solvents is still based on very time consuming and costly experiments. Thus, robust predictive electrolyte thermodynamic models are required to drastically reduce the experimental effort.

In this work, ePC-SAFT was used to predict the phase equilibria for the absorption of the sour gases CO_2 and H_2S in an aqueous blend of MDEA and sulfolane. The following five reactions were taken into account:

$$H_2O \rightleftharpoons OH^- + H^+ \quad (1)$$
$$MDEA + H^+ \rightleftharpoons MDEAH^+ \quad (2)$$
$$H_2S \rightleftharpoons HS^- + H^+ \quad (3)$$
$$CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+ \quad (4)$$
$$HCO_3^- \rightleftharpoons CO_3^{2-} + H^+ \quad (5)$$

Correctly predicting the experimental data requires simultaneously solving these reactions as well as vapour-liquid equilibria. Figure 1 shows the amount of absorbed CO_2 as function of its partial pressure in the aqueous blend for 313 K and 373 K, while in Figure 2 the amount of one sour gas in presence of the second one is illustrated. Sour gas concentration is depicted as moles gas absorbed per mole employed amine (loading α).

For all systems, ePC-SAFT predictions are in excellent agreement with the experimental data.

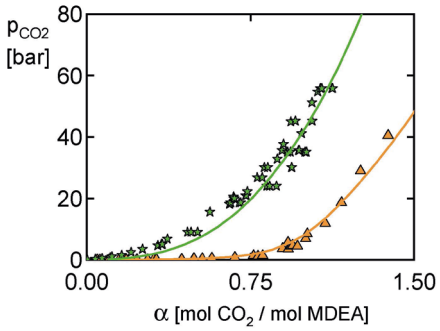

Figure 1: Amount of absorbed CO_2 in the aqueous solvent blend 20.9 wt % MDEA and 30.5 wt % sulfolane at 313 K (orange) and 373 K (green) for different CO_2 partial pressures. Symbols are experimental data, lines are ePC-SAFT predictions.

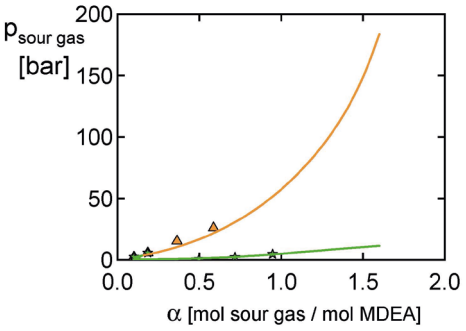

Figure 2: Amount of selectively absorbed sour gas in mixed aqueous solvent of 20.9 wt-% MDEA and 30.5 wt-% sulfolane. Symbols are experimental data, lines are ePC-SAFT predictions
Orange: CO_2 in presence of H_2S (α_{H2S}=0.35, T=313 K)
Green: H_2S in presence of CO_2 (α_{CO2}=0.35,T=373 K).

Thus, as a robust model, ePC-SAFT can be used to predict sour gas absorption even in highly complex systems containing electrolytes. This will help to reduce the experimental effort for discovering new solvent blends drastically.

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Rapid Identification of an Extraction System for the Purification of Enzymes

Identifying tailor-made aqueous two-phase system for industrially relevant biocatalysts

Maximilian Wessner, Gerhard Schembecker, Christoph Brandenbusch

Industrial relevant enzymes have reached industrial competitiveness over classical chemical catalysts due to gentle operating conditions and high specificity for the substrate. Within their production, the purification of the enzyme using Aqueous Two-Phase Extraction (ATPE) has been shown to be a promising alternative to time- and cost-intensive chromatographic separation. Within this work, we applied an optimized method to identify tailor-made Aqueous Two-Phase Systems (ATPS) to be used in ATPE. It was shown, that for an industrially relevant enzyme (that is Chimera [supplied by Georgia Tech, Bommarius Lab]) it was possible to identify a suitable ATPS as well as a process window for the ATPE in less than three weeks. With achievable yields above 78%, the possibility to influence the partitioning behavior of Chimera, this system outclasses the previously randomly selected ATPS (Trial-and-Error High Throughput Screening) by a factor of four, at the same time keeping precipitation of the enzyme below 17% (previously 70%).

The optimization of the downstream processing of biomolecules (this work: enzymes) has often been neglected. Thus, up to 50-60% of the total production costs attributed to the downstream processing. ATPE using an ATPS offers a valuable alternative to classical “standard” chromatography. ATPS consist of two phase formers dissolved in water above a critical concentration, generating two (immiscible) liquid phases. However, ATPE has not yet made it to industrial application, because selection of an appropriate ATPS is often based on time and cost-intensive high-throughput screening. To solve this challenge, we developed a method combining thermodynamic modeling and a small set of experiments to select phase formers and process conditions that create a tailor-made ATPS. Within this work, the method was applied for the purification of a previously unknown enzyme (Chimera) considering sodium citrate (Na_3Cit), sodium glutamate (NaGlu), polyethylene glycol 2000 (PEG2000) and polypropylene glycol (PPG400) as phase formers.

In a first step, thermodynamic modeling and investigations on the conformational biomolecule stability in the presence of the respective phase formers (using the unfolding temperature $T^{Unfolding}$) used to pre-select suitable phase formers.

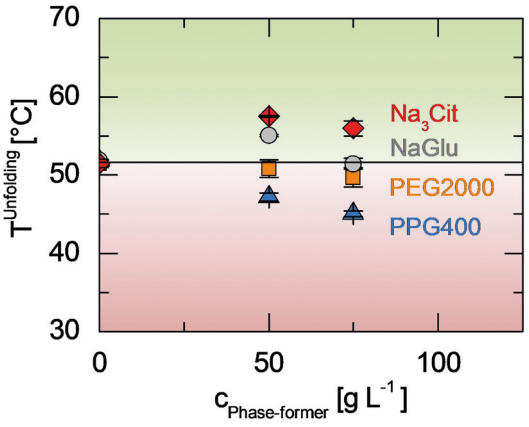

Figure 1: $T^{Unfolding}$ of Chimera in aqueous solutions with different concentrations of the phase formers PPG400, PEG2000, NaGlu and Na_3Cit at pH 7 and 1 bar.

The biomolecule stability is decreased, if a phase former drastically decrease $T^{Unfolding}$ upon increasing phase former concentration as seen for PPG400 in Figure 1. This excludes the phase former from being a potential phase former candidate. Next, the colloidal stability of the biomolecule is investigated by measuring biomolecule-biomolecule interactions estimating the aggregation propensity in presence of the phase formers. Therefore, the diffusion-interaction parameter (k_D) was measured (Figure 2) using dynamic light scattering.

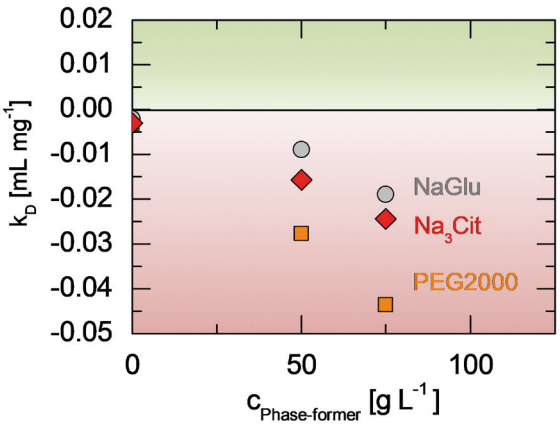

Figure 2: k_D of Chimera in aqueous solutions with different concentrations of the phase formers PEG2000, NaGlu and Na_3Cit at pH 7, 298.15 K and 1 bar.

Positive (negative) values indicate repulsive (attractive) interactions between biomolecules. Attractive interactions cause aggregation and thus strongly negative values are undesirable. With respect to the results shown in Figure 2, NaGlu is thus favored over Na_3Cit. In the subsequent ATPE, a Chimera yield of 78.7% was achieved being a four-fold improvement to the previously randomly selected ATPS (ammonium citrate - PEG4000 ATPS). Prospectively, this method will support the integration of ATPE in downstream processing of biomolecules by reducing the effort for ATPS development.

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Thermodynamics of Glycolysis

New standard Gibbs energy of reaction values for glycolysis reactions determined from equilibrium measurements combined with activity coefficients

Thorsten Greinert, Gabriele Sadowski, Christoph Held

For many organisms, glycolysis is a central metabolic pathway that provides energy and synthesis of precursors for further biosyntheses. The reaction equilibria of the single glycolytic reaction steps was investigated in this work to gain new thermodynamically-consistent standard data. The availability of such new data allows applying systems-biology tools for future investigations of the feasibility of the pathway, or parts of it, in a cell or even in a bioreactor.

Within glycolysis, one mole of glucose is converted in ten reaction steps to two moles of pyruvate. For this, two moles of adenosine diphosphate (ADP), phosphate (P_i) and nicotinamide adenine dinucleotide (NAD^+) are required, finally yielding two moles of each of the products adenosine triphosphate (ATP), the reduced form of NAD^+ (NADH), H^+ and water. The net gain of two moles ATP and two moles NADH makes glycolysis so important for the energy production of a cell.

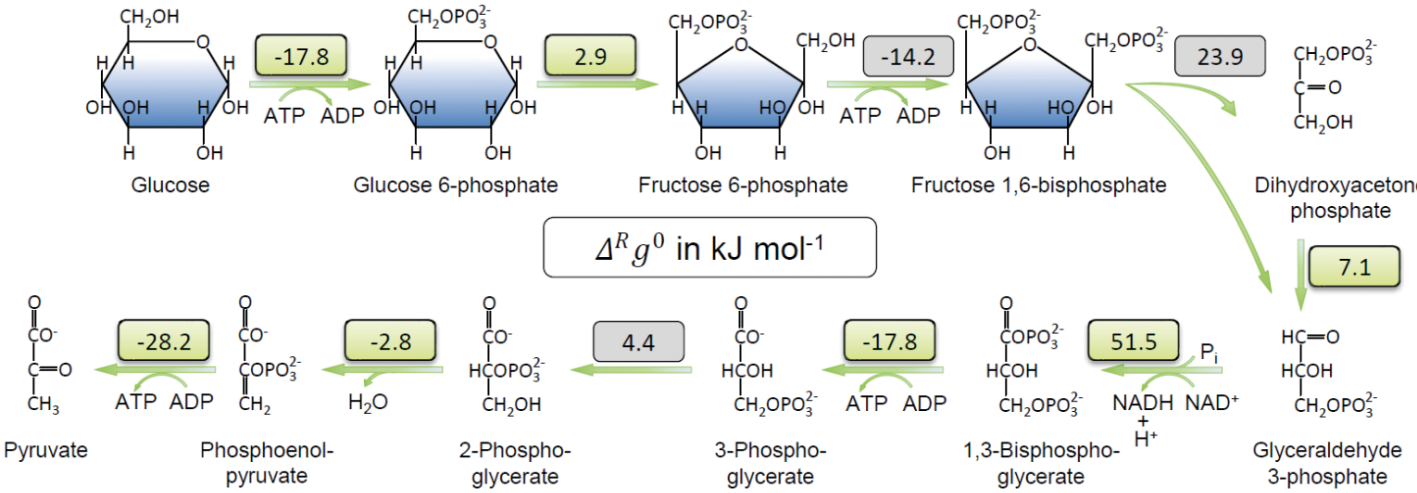

Figure 1: New (green) standard Gibbs energy of reaction values $\Delta^R g^0$ for the ten reaction steps of the glycolytic pathway at 298.15 K and 1 bar.

This energy gain depends on the reaction conditions. Therefore, researchers have investigated the feasibility of glycolysis at reaction conditions in a cell or in a bioreactor. Such feasibility analyses require a thermodynamically correct standard Gibbs energy of reaction $\Delta^R g^0$. This can be calculated from the activity-based thermodynamic equilibrium constant K_a:

$$\Delta^R g^0 = -RT \ln(K_a) = -RT \ln(K_{exp} K_\gamma) \qquad \text{(Eq. 1)}$$

K_a is calculated in this work from the ratio of the product and reactant concentrations K_{exp} and the ratio of the activity coefficients of products and reactants K_γ. K_{exp} is accessible by equilibrium measurements of the single reaction steps and analysis of the concentrations. K_{exp} depends on the reaction conditions chosen for the measurements, i.e. temperature, pressure, and the composition of the media. This includes concentration and type of buffers, salts or other co-solutes and even the concentration of the substrates. In literature, the concentration-dependent K_{exp} values were used instead of K_a to determine standard Gibbs energies of reaction. However, this is not correct as K_{exp} values are valid at very specific conditions only. This leads to misinterpretations of feasibility analyses. In this work K_{exp} was remeasured for the ten reaction steps; further, K_{exp} values were combined with K_γ values obtained from the thermodynamic model ePC-SAFT yielding the activity-based K_a value and thus consistent $\Delta^R g^0$ values. These new $\Delta^R g^0$ values were determined for all glycolytic reactions shown in Figure 1. This contributes to the full thermodynamic description of the glycolytic pathway at any desired conditions.

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Predicting the Supersaturation Behavior of Indomethacin in Aqueous Solution

Interplay of kinetics of dissolution, recrystallization, and solid-state transformation

Raj Schneider, Jana Kerkhoff, Andrijan Ohmann, Gabriele Sadowski

Amorphous formulations of active pharmaceutical ingredients (APIs) represent a valuable tool towards addressing the ever-existing challenge of bioavailability limitation during administration of poorly water-soluble APIs. Yet, it has often been observed that formulations with proven long-term stability - even at high relative humidity - only performed superior to their crystalline counterparts for a much shorter period than expected when subjected to dissolution tests. The mechanisms at play – dissolution, solution crystallization, and solid-state transformation-, while generally not unknown to the scientific community, were assessed and combined quantitatively for the first time in this work.

Goal of this work was to develop individual kinetic models for dissolution, solution crystallization, and solid-state transformation of indomethacin (IND) in aqueous solution. Each model was parameterized by fitting independent kinetic data. The models were integrated with one another to make predictions for supersaturation profiles when these mechanisms occur simultaneously. Figure 1 visualizes this concept.

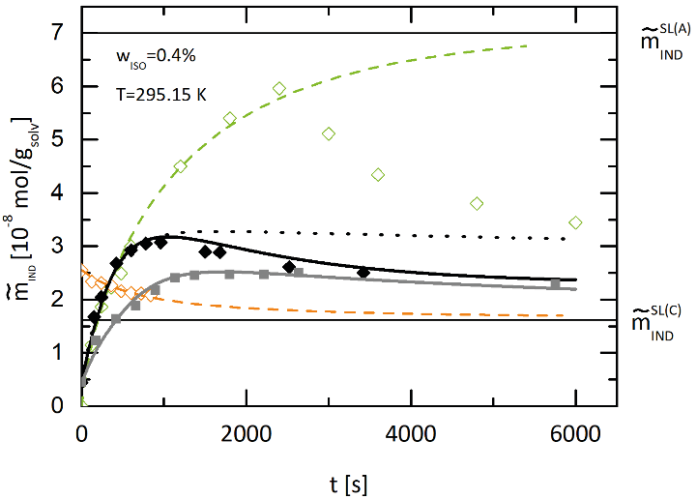

Figure 1: Dissolution (green), desupersaturation (orange) and supersaturation (black) profile of 30 mg amorphous IND in the presence of 9 mg crystalline IND seeds at 295.15 K and 460 rpm in aqueous solution containing 0.4 wt% isopropanol (ISO). Squares and diamonds represent experimental data. Dashed lines represent fits to separate kinetic models for dissolution and desupersaturation. Dotted lines represent predictions of supersaturation profiles without accounting for solid-state transformation, while the solid lines include these kinetics. The supersaturation profile of 20 mg amorphous IND is shown in grey.

Dissolution and desupersaturation profiles were measured in this work and fitted to a chemical-potential-gradient model. Solid-state transformation kinetics represented by amorphicity functions *φ(t)* were derived from literature data and compared with own measurements. For the first time, such kinetics were quantitatively evaluated. Interestingly, as can be seen in Figure 2, data from independent sources (infrared spectral analysis, intrinsic dissolution rate measurement) yielded very similar kinetics. Moreover, in contrast to the results obtained from long-term stability test performed at high relative humidity (up to 98%), such transformations seem to occur on the time scale of minutes rather than days. It was found that when accounting for such transformations in the kinetic modelling, surprisingly accurate predictions are obtained. Conversely, when disregarding the solid-state transformation, the supersaturation profile is substantially overestimated. This shows that solid-state transformation causes the therapeutic window of application to be considerably shorter than one would expect. Inhibiting this transformation represents a key element when tuning the enhancement of bioavailability. The proposed model was successfully validated for robustness under different conditions, such as different amounts of amorphous and crystalline solid as well as solvent compositions.

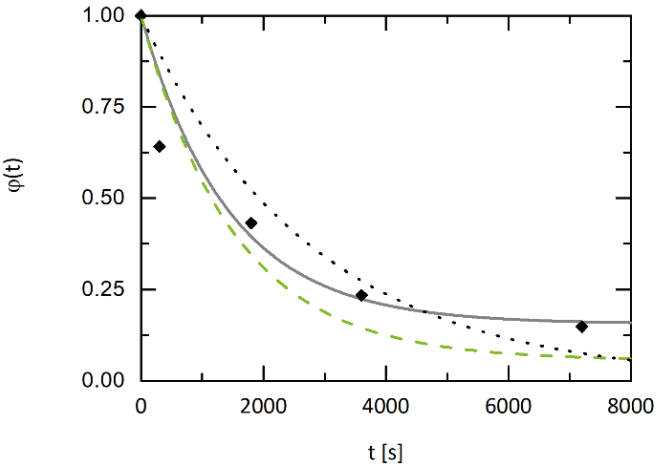

Figure 2: Amorphicity function *φ(t)* of amorphous IND in aqueous solution at 295.15 K. The black squares represent evaluation of infrared spectral data taken from the literature. The grey, solid line and green, dashed line represent evaluations of intrinsic dissolution rate measurement at different flow rates taken from the literature. The black, dotted line represents an evaluation of intrinsic dissolution rate measurement performed within this work.

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Solvent Impact on the Product Quality of Pharmaceutical Formulations

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The production of polymer-based pharmaceutical formulations often involves solvent-based processing steps such as spray drying. In order to obtain homogeneous and stable formulations, any changes, like crystallization of the active pharmaceutical ingredient (API) or phase separation of the components involved must be avoided. The phase behavior during drying must be known for successfully drying the formulation from a solvent or solvent mixture. The proposed method for the first time enables identifying appropriate solvent candidates for the production of ASDs with significantly less experimental effort than before.

The aim of this work was to develop a thermodynamic approach that predicts the phase behavior of so-called amorphous solid dispersions (ASDs) and their drying curves using PC-SAFT to predict and to avoid unwanted ASD phase changes during drying. Identifying completely miscible polymer/solvent mixtures is the first important step towards a solvent-based ASD production, whereby in the second step it must be clarified whether the mixture remains homogeneous during the entire drying procedure. In cases where API and polymer are not soluble in one common solvent, solvent mixtures are used. Due to the different volatilities, the evaporation of the individual solvents varies. The ASD/solvent mixture therefore follows curves rather than straight lines across the phase diagram during drying, eventually reaching the solvent-free ASD.

Hydroxypropyl methylcellulose acetate succinate (HPMCAS) is a highly popular polymer for ASDs. It is one of those candidates, which needs to be spray dried from solvent mixtures, because it is not completely miscible with any of the solvents used in pharmaceutical production. To find a suitable solvent mixture for HPMCAS, first the phase diagram and the drying curves were calculated for HPMCAS ASDs and then validated experimentally via Raman spectroscopy. For an ASD consisting of naproxen (NAP) and HPMCAS, the predicted phase behavior and drying curves are shown for ethanol/water (Figure 1a) and acetone/water (Figure 1b) solvent mixtures. Starting from a homogeneous liquid phase in which both, API and polymer, are completely dissolved, the miscibility gaps and drying curves look quite different for the two solvent mixtures. The system with the ethanol/water mixture was predicted as being appropriate for the investigated ASD, since no phase separation occurred along the drying curve. In contrast, the use of an acetone/water mixture led to unwanted phase separation during drying. Furthermore, the solubility line was exceeded in both systems for ASD concentrations w_{ASD}>0.4, which led to NAP crystallization.

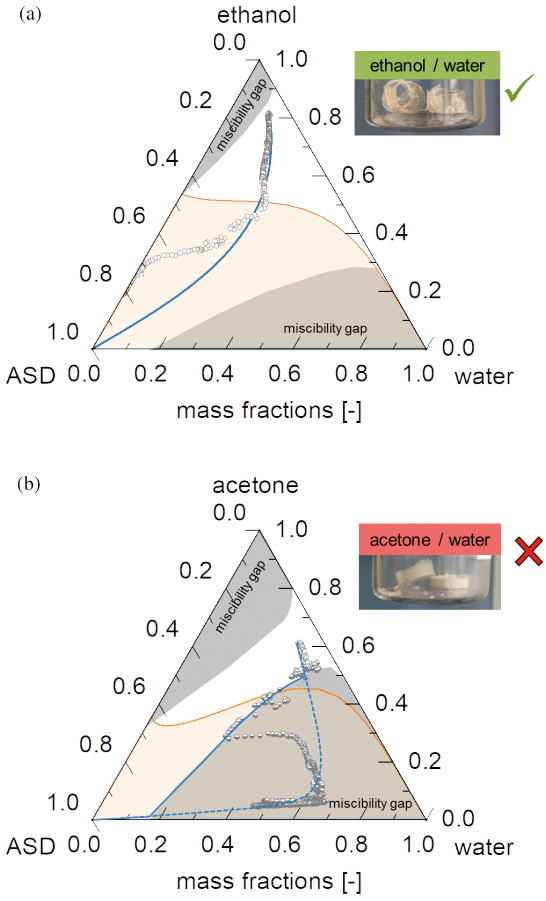

Figure 1: Drying of a NAP/HPMCAS ASD (wNAP = 0.15 in the ASD) from (a) an ethanol/water mixture and (b) an acetone/water mixture at 25°C. PC-SAFT calculated phase diagrams show miscibility gaps (gray regions), the solubility lines (orange lines), the predicted drying curves (blue lines) and the experimentally-observed liquid compositions (points) during drying.

The prediction of unwanted phase separation and NAP crystallization during ASD drying from solvent mixtures was in perfect agreement with the experiments. PC-SAFT thus allows for correctly identifying suitable solvent mixtures and even the best solvent-mixture ratios required for preparing and drying ASDs without any experimental effort.

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