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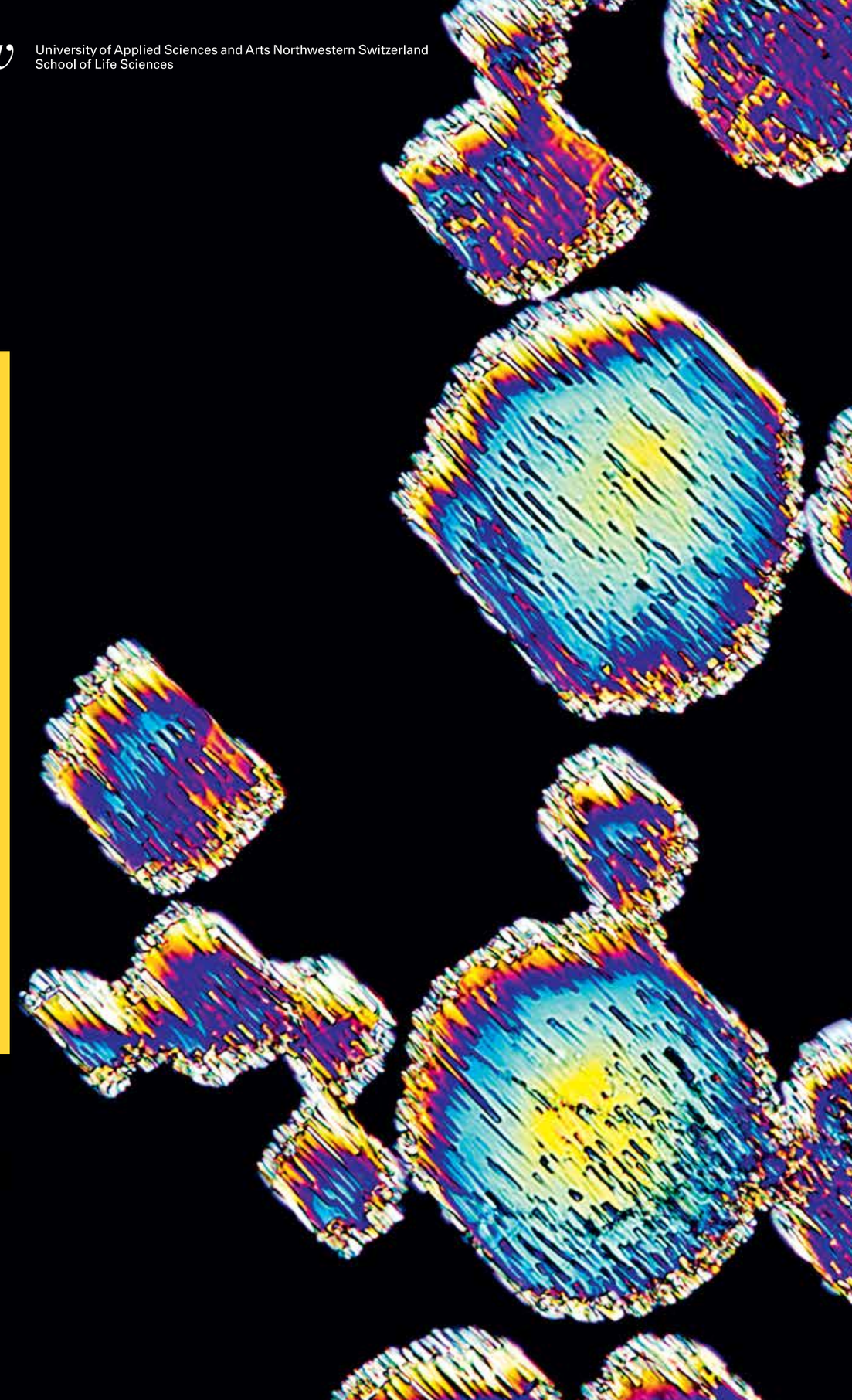
Research Report
2011/2012



Editorial

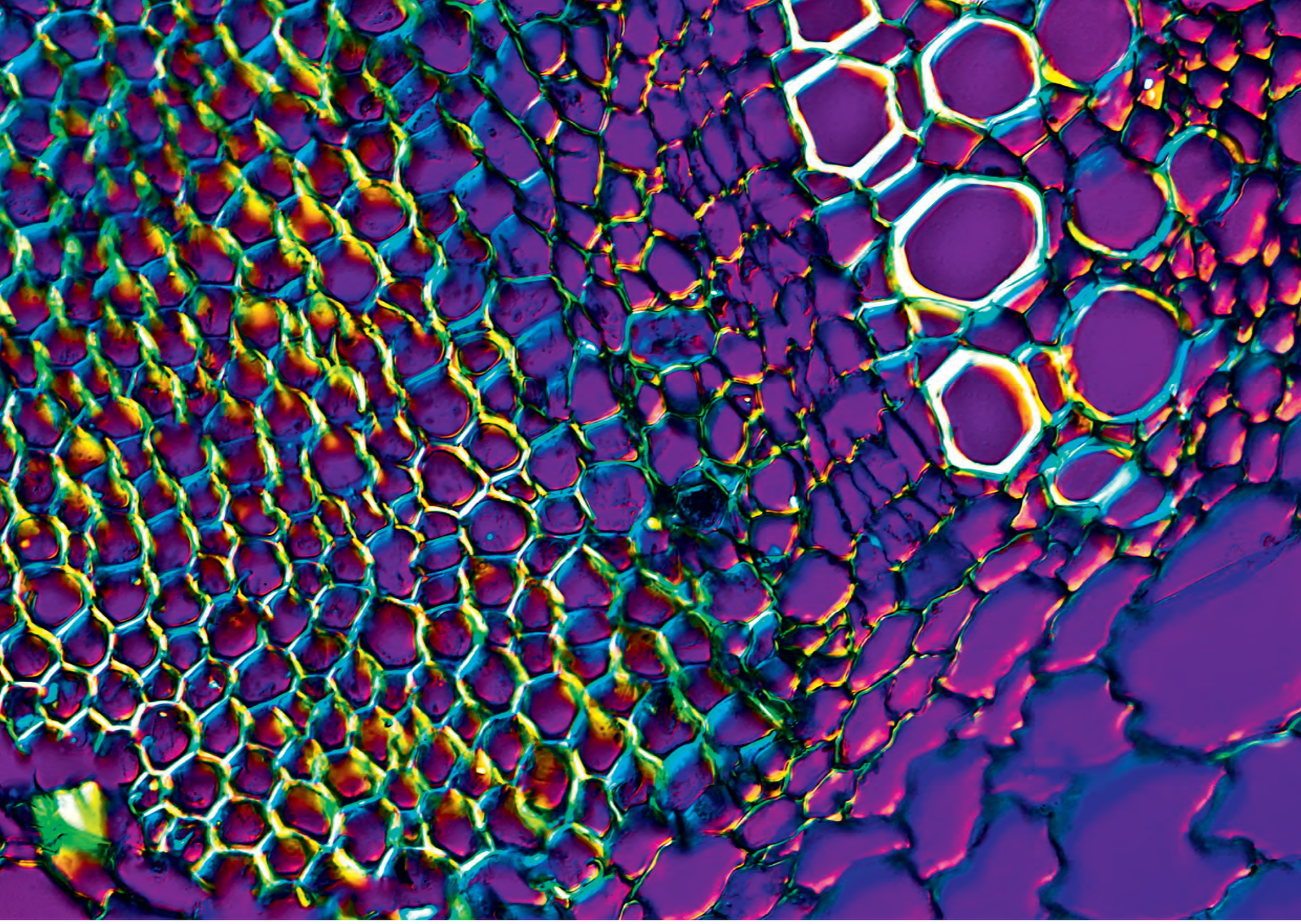
"Higher Education, Research and Entrepreneurship" are guiding principles of the School of Life Sciences FHNW. In our understanding well trained professionals, innovative ideas combined with solid scientific knowhow and a mindset to application are the basis for successful outcome of "applied" research. In this sense research is a cornerstone at the School of Life Sciences FHNW.

The present report provides an insight into our research. It covers three main areas "Molecular Technologies", "Therapeutic Technologies" and "Environmental Technologies". These are handled jointly by our institutes. The described projects range from comprehensive disease diagnosis, development of innovative healthcare products and procedures for sustainable manufacturing and environmental solutions. In fact, technology development is central in our research. It opens up ways to new Life Sciences products, to industrial process innovations and to novel environmental solutions. A good example is chemical sensing as described in two projects or bio-nanotechnology and material sciences used for biomedical and medtech product development. Sophisticated analytical technologies may even lead to novel healthcare products as illustrated by the bamboo project. Finally, the increasing importance of environmental problems/issues can be addressed using bio-technology and process technology, e.g. for wastewater treatment or for gaining materials from renewable resources.

Our researchers collaborate closely with industry – regionally, nationally and internationally. The success of the technology transfer is shown by many projects directly funded by industry or co-funded with the Commission for Technology and Innovation CTI. Successful funding trough Swiss National Science Foundation and the European FP7 Program further shows the attention to interdisciplinary projects and inclusion of academic partner which is crucial for those agencies. Finally, we are happy that first spin-off companies evolve from our research.

Overall, the development of our research activities is very positive. I hope you enjoy reading this report.

Gerda Huber
Director, School of Life Sciences FHNW



Molecular Technologies (MT)
Technologies for the synthesis and analysis of active compounds and biological systems

Novel viscosity- and density-meters for process monitoring and biomedical sensing applications

The NoViDeMo project investigates application of nanomechanical resonators (cantilevers) for real-time viscosity and density measurements in biomedical research and industrial applications. Here real-time chemical polymer-reaction measurements were studies in order to monitor the degree of polymerization.

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Keywords: Microcantilever, micro-viscometer, sensing, polymer characterizations

Introduction

Development of a nanomechanical real-time viscosity- and density-meter is a challenge for small fluid volumes, as well as applications of such sensor in industry and biomedical research. Here micro-cantilevers are operated in a dynamic vibration mode to measure the properties of fluids in volumes down to 10µl (Fig. 1). This sensing principle is developed for two main applications:
(i) New **in-line viscosity and density sensors** for process-monitoring and quality control of test liquids. The general performance of the sensor, such as its resolution, dynamic range and liquid compatibility, will be evaluated according to industrial needs (Endress+Hauser, Flowtec AG). Furthermore, a chemical polymer-reaction measurement in real-time is studied to monitor the degree of polymerization. Here the polymer characterization with the Microcantilever is described.
(ii) New **sensing platform** for analytical detection and activity tests. The sensor is studied for specific stimulus-responsive polymer-based detection of glucose.

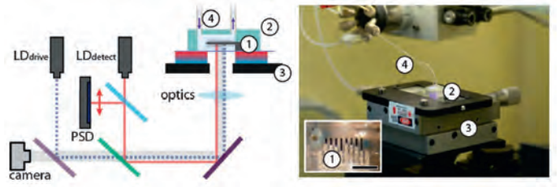

Figure 1 *Schematic and photograph of the improved exprerimental setup. To drive and detect the vibration of microcantilevers a modulated laser and an optical beam deflection system are used. The cantilevers (1) are immersed in a µL fluid cell. The fluid cell (2) is fabricated from PDMS and bond onto a temperature controlled (15–40°C) glass slide mounted on an xy-stage (3). The samples are injected through tubing connected to a valve equipped with two 10 µL sample-loops (4).*

Viscosity and density are important liquid characteristics and are highly sensitive to the composition and physical state of the fluid. However, real time-measurement of these properties is still challenging, especially for small sample volumes below 40µl.
Current commercial micro-viscometers need sample volumes of at least 50µl and do not provide in-situ viscosity information [1]. Several publications discuss the use of micro-fluidics for rheological measurements. These methods are based on differential-pressure measurements [2,3], or microscopic particle tracking in micro-channels [4]. Unlike cantilever sensors these alternatives do not provide simultaneous information on the viscosity and density. Currently, no commercial instrument based on these techniques is available. The only technology for label- and functionalization-free sensing of molecular interactions is micro-calorimetry; the smallest volume in commercial instruments is 190µl and is used by Nano ITC.
No commercial cantilever based system for viscosity and density measurements is known; however, in recent years research in this direction has accelerated. A first prototype of a cantilever based real-time viscosity- and density-meter was developed within an SNF project (NSX1003 granted to TB and Chr. Gerber, SNI). Here the development of a real-time sensor, simultaneously detecting the viscosity and density of fluids is planned. We used micro-cantilevers operated in a dynamic vibration mode and evaluated the response spectra of the excited cantilevers to extract viscosity and density values.
The application of this new sensor is important in various industrial scenarios. The small sample volumes required for measurements allows further miniaturization of test production. Or even the implementation of this technology on a lab on a chip. One particular application is monitoring of the polymerization level of a chemical reaction, to stop the reaction at a desired polymer length.
Polymer characterization measurements were used in order to explore the potential and limitations of the sensor device.

Results

For applications in research, e.g. biology and chemistry, the setup has several advantages: it is a new sensing principle for analytical detection and activity tests. Currently, most molecular sensors rely on fluorescent or mass sensitive detection methods. Within this study, we explore a novel readout mechanism by monitoring viscosity changes due to alterations in the folding state of receptor functionalized polymers in solution upon interaction with their respective analytes. The viscosity changes with the concentration, folding and aggregation state of dissolved molecules, e.g. of proteins and polymers. These micro-viscometers are a novel sensing platform for the detection of molecular interactions. The study of polymer characterizations targets two questions: first, the time-resolved study of viscosity during chemical polymerization reaction and second, the characterization of polymers synthesized using the controlled radical polymerization, mainly to determine the molar mass of the polymers. For this second subproject, the focus is on cationic polymers; these polymers are difficult to analyse with classical characterization methods.

For the first step, real-time measurements of acrylamide (Aam) polymerization were successfully performed (Fig. 2). For this experiment, sample was continuously extracted from a larger reaction vessel by a pump through the measurement chamber. Note the change in the polymerization rate (black arrow). For interpretation of this regime change, two possible explanations were found in the literature. The change in slope (arrow) could indicate a regime change with different concentration-viscosity behavior. Alternatively, the kinetic changes are due to the temperature increase from the exothermic reaction. This could also explain the slight decrease in the liquid density. Note that the viscosity shift is about 250% whereas the density stays within 2% of the initial value. Future polymerization experiments will be performed in the temperature controlled instrument using fused silica capillaries as reaction vessels. This will allow a precise temperature control and facilitate data interpretation.

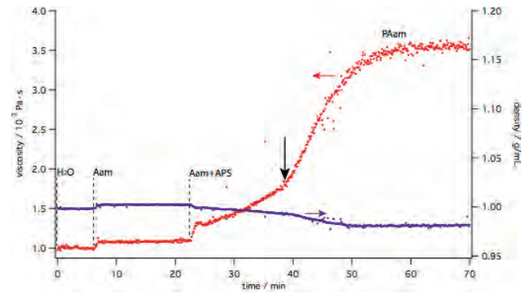

Figure 2 *Polymerization of acrylamide. After recording a baseline in water (H_2O) and acrylamide monomer (Aam) the reaction is initiated with ammonium persulfate (APS). The increase in viscosity indicates ongoing polymerization into polyacrylamide (PAam).*

In macromolecular chemistry, the characterization of a cationic polymer and especially the determination of its molar mass are problematic. The determination of molar mass and polydispersity of polymers are usually studied by size exclusion chromatography. However, for a cationic polymer this method is not trusted, because of the electrostatic attraction between the cationic charge and the separation column material. Alternatively, viscosimetry is used applying the Mark–Houwink model. To this end, the intrinsic viscosity of the polymer solution is determined. For our study, we developed protocols and synthesized test materials using the atom transfer radical polymerization (ATRP) of two different monomers (Fig. 3): The first cationic, [2-(methacryloyloxy) ethyl]-trimethylammoniumchloride (MeDMA)[5], and the second neutral, 2-hydroxyethyl methacrylate (HEMA). These two monomers were chosen for several reasons: (i) the difference in the chemical structure based on the quaternary ammonium introducing a positive charge in one of the monomers, (ii) the same polymerization method (ATRP) of the two monomers, (iii) easy synthesis, (iii) the neutral polymer will provide a good "positive sample", which can be analyzed with standard methods for comparison. We are now compare the results between micro-viscometery and SEC analysis and the potential effect of the high measurement speed in our micro-viscometer. These experiments are currently being completed.

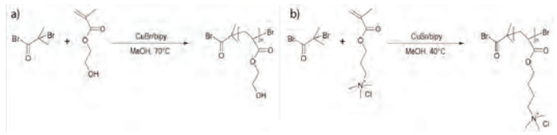

Figure 3 *ATRP polymerization reactions. a) Polymerization of 2-hydroxyethyl methacrylate, a neutral monomer (HEMA); b) polymerization of the cationic [2-(methacryloyloxy)ethyl]-trimethylammoniumchloride (MeDMA) monomer.*

Conclusion and outlook

The in-situ characterization of chemical polymerization reactions was investigated. These experiments are ongoing. The results obtained so far show that the new sensor allows characterization of the polymerization growth in real-time. The kinetics of the polymerization also shows two kinetic regimes, depending on the degree of polymerization. The obtained results suggest that the micro-viscometer will be able to characterize the behaviour of stimuli responsive polymers and their application as (bio)sensors.

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Research Focus Area:
Molecular Technologies (MT)

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Partners
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Funding
Swiss Nanoscience Institute (SNI)

Economic efficiency and benefit to society

Sensitive and precise density and viscosity measurements are important for e.g. quality control of medical formulations to ensure their safety and efficacy. Furthermore the presented measurement method has the potential to increase the workflow in chemical research laboratories. Finally, the presented sensor systems may be used for medical diagnostics, e.g. early detection of neurodegenerative diseases.

Biomimetic membranes from supported block copolymers and Aquaporins for environmental sensing applications

Synthesis of chemically stable and mechanically robust biomimetic membranes was investigated as new materials for applications in environmental engineering. The membranes are based on amphiphilic block copolymers and embedded Aquaporins immobilized on nanoporous alumina substrates. These novel systems will provide highly selective water membranes that allow desalination and production of pure water.

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School of Life Sciences FHNW

Keywords: Biomimetic Membranes, Block Copolymers, Aquaporins, desalination, water purification.

Introduction

A decline in water supplies and the growing demand for fresh water is a motivation for desalination of seawater. The conventional membranes treatment processes for sea desalination are energy intensive and water recovery is often limited. Biomimetic membranes are designed to mimic the highly-selective water transport across cell membranes. One promising biomimetic membrane technology employs natural proteins called aquaporins to regulate water flow. Aquaporins are biological water channel proteins that provide a selective and rapid transport of water across cell membranes. It acts as water channels which selectivity allows water molecules to pass through while the transport of ions, protons and hydroxyl ions is prevented. The result is that only water molecules, and nothing else, can pass through aquaporin water pores. The understanding of aquaporins and their role as water channels has opened up the possibility to use this technology in water purification and in an industrial context. However, the use of aquaporins in a biomimetic filter membrane requires a suitable support material to stabilize the biomimetic matrix against hydraulic pressure forces. In order to address this, new kinds of supported bio-artificial compounds suitable for making stable protein incorporation membranes are required.

The membrane formation and protein incorporation have been explored by the group of Prof. Meier from the University of Basel [1, 2]. They used an ABA amphiphilic block copolymer for the synthesis of a free-standing stable membrane, suitable to accommodate active membrane proteins in a hydrophobic environment.

Taking the work of Meier's group as a starting point [3], this project aims to combine stable synthetic membranes based on amphiphilic block copolymers and naturally occurring proteins, i.e. aquaporins. Aquaporins were incorporated into synthetic biomimetic polymer supported membranes and their potential in water purification desalination is currently being investigated.

Methods and Results

The project is a multidisciplinary approach to develop biomimetic membranes for applications in environmental engineering.

The main idea is based on the use of biological water channel Aquaporins and artificial membranes for the fabrication of new hybrid materials for industrial application in desalination and water purification. These systems could provide highly selective water membranes that allow the production of pure water or salinity power. The incorporation of AqpZ (Aquaporins) into block copolymer membranes will produce membranes requiring substantially less energy to achieve the same water flux and selectivity as existing water treatment membranes The synthesis and the study of this membrane is based on three main steps. 1: The synthesis of amphiphilic block copolymer membranes and embedded aquaporins, immobilized on nanoporous alumina substrates. 2: The effective incorporation of Aquaporins in this membrane. 3: The study of membrane capacity and effectiveness in water filtering devices. The biomimetic membranes designed from supported type ABA amphiphlic block copolymers and aquaporins is detailed in figure 1.

Figure 1 *Schematic design of Biomimetic membranes designed from amphiphilic block copolymers and Aquaporins*

The membrane is based on nanostructured alumina surfaces (Fig. 3-a) covered with a layer of amphiphilic triblock copolymer poly(2-methy-2- oxazoline)-b-polydimethylsiloxane-b-poly(2-methyl-2-oxazoline) (PMOXA-PDMS-PMOXA) containing aquaporins. The first step was the functionalization of the nanoporous alumina with an active site, a "cross-linker group" allowing a covalent link between the block polymer and the alumina surface. The activation of the nanoporous alumina was obtained by the grafting of methacylate groups onto the surface. The second was the polymer synthesis (Fig. 2-a); the PMOXA-PDMS-PMOXA block copolymers were synthesized and self-assembled into polymer vesicles acting as containers for aquaporins (Fig. 2-b).

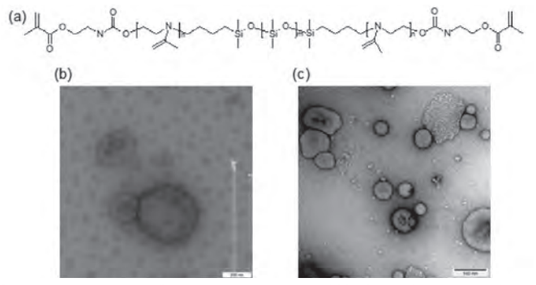

Figure 2 *a) Structure of (PMOXA-PDMS-PMOXA) block copolymers terminated with methacrylate b) Transmission Electron micrograph of $PMOXA_{20}$-$PDMS_{41}$-$PMOXA_{20}$ vesicles, self assembled structures from the amphiphilic block copolymers c) TEM of vesicles incorporated Z-aquaporins.*

The polymer was incorporated on the surface with a "grafting to" method on which vesicles were linked to the surface with a coupling reaction between the surface and the polymer under UV light. The study of the SEM pictures (Fig. 3-b) shows that the vesicles were open on the surface and filled the alumina pores homogenously. The incorporation of polymer vesicles containing aquaporins on the nanoporous surface allowed a uniform filling of the pores.

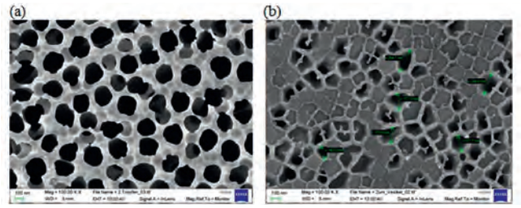

Figure 3 *a) SEM picture of unmodified nanoporous alumina with an average size pore of 200 nm, b) SEM picture of polymer modified nanoporous alumina*

Conclusion and outlook

The development of nanostructured alumina surfaces covered with a layer of amphiphilic triblock copolymer embedded with aquaporins was investigated.

The characterization and the activation of "nanoporous alumina" support membranes were studied. For the polymer synthesis, the poly(2-methy-2-oxazoline)-b-polydimethylsiloxane-b-poly(2-methyl-2-oxazoline) (PMOXA-PDMS-PMOXA) block copolymers were synthesized and self-assembled into polymer vesicles acting as containers for aquaporins. Vesicles were incorporated on the surface with a grafting to approach. The polymer and the surface were end terminated with a methacrylate group allowing coupling reaction under UV light and controlled pressure. The uniformity and stability of the polymer layer on the solid surface is one of the crucial points that established the parameters.

On the other hand, the result of the incorporation of vesicles in the nanoporous alumina surface with size pores of 200 nm was very promising and unexpected. No vesicles are observed on the surface, meaning that they were open on the surface and filled the alumina pores homogenously. The incorporation of the vesicle on the alumina surface to the pores was complete. To the best of our knowledge, this is the first time that incorporation of vesicles on a porous surface has allowed a uniform filling of the pores.

The potential in water purification of the developed membranes is currently being investigated.

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Research Focus Area:
Molecular Technologies (MT)

Project Team:
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Partners:
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Funding:
Swiss National Science Foundation (SNSF) and Swiss Nanoscience Institute (SNI)

Economic efficiency and benefit to society:
Fresh water has a huge market potential with annual turnovers >1 billion CHF. The impacts of this project will be the development of a sustainable membrane for water desalination.

Optimized fluoride nanoparticles for dental care

Fluoride is a widely accepted compound in dental care for the reduction of enamel eroding processes. Calcium fluoride particles have been synthesized which adhere to enamel surfaces and which can serve as constant release devices to maintain increased fluoride levels in the time intervals between applications of dental care products.

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Keywords: dental care, fluoride particles, adhesion, release

Introduction

The use of fluoride-containing dental care products has a beneficial effect on the reduction of tooth enamel destroying processes such as caries and erosion. The mode of action of fluoride is twofold: while high concentrations of fluoride during dental care result in the incorporation of this fluoride as more acid resistant fluorapatite into the surface layer of the tooth enamel, constant low concentrations in the intervals between the applications positively influence the enamel de- and re-mineralization cycles [1].
On the enamel surface of teeth treated with soluble fluoride ions calcium fluoride (CaF_2) particles are formed which could serve as reservoirs for fluoride in the time intervals between the applications [2]. Little is known about the formation of these particles, nor about their adhesion to the tooth enamel and their dissolution over time, especially during cariogenic and erosive challenges. The aim of the project presented here is (I) to gain more insights into the CaF_2 particle formation process and (II) to optimize these particles with respect to enamel adhesion and fluoride release kinetics.

Results

The first step of the project was the investigation of the structural flexibility of CaF_2 particles and the possibilities to influence their crystallization. For pharmaceutical companies such knowledge is very valuable since the crystal structure of active ingredients can influence their dissolution behaviour and tissue interaction. Modelling results from the group of S. Goedecker at the University of Basel suggested that small CaF_2 assemblies can exist in different amorphous states, whereas for larger systems, crystal structures with (111) planes are favoured, which would result in octahedral particles. In this study we were able to generate in situ such octahedral CaF_2 particles, however additional different morphologies can be achieved by tuning the mixing ratio of soluble calcium and fluoride ions. Particles ranging from approximately 50 nm to several µm in diameter can be produced. Their shapes range from perfectly cubic to more octahedral and round. Figures 1a-1d show the appearance of some of these particles by scanning electron microscopy (SEM). The systematic investigation of the effect of the concentrations of calcium and fluoride ions during synthesis on the shape of the final particles are summarized in Fig. 1e. Generally, larger particles are formed at lower concentrations and in some instances intermediates between different shapes can be observed, as e.g. when at a fixed fluoride concentration of 4 mM and calcium varying between 10 mM and 120 mM the particles change from cubic to round.

The strength of adhesion of the synthesized CaF_2 particles to tooth enamel is another major criterion for their designated application as fluoride storage forms and is investigated together with our project partners from the group of E. Meyer at the University of Basel. They applied AFM (atomic force microscopy) based methods to determine the adhesion of individual CaF_2 particles to the enamel surface. Comparing different particles' geometries, strong adhesion was observed for cubic particles with diameters in the range of 50-100 nm (see Fig 1a). In collaboration with the Department of Preventive, Restorative and Pediatric Dentistry University of Bern the interaction of these particles with tooth surfaces was analyzed by SEM. CaF_2 particles were applied in concentrations corresponding to the fluoride concentrations typically present in dental care products like toothpastes and mouthrinses. Particles adhere to intact as well as initially damaged tooth enamel which would allow their use for both prevention of enamel erosion and repair (Fig. 2).
Fluoride ions have been demonstrated to support the re-mineralization of damaged tooth enamel in concentrations as low as 0.05 ppm and studies report lower caries incidence in individuals with salivary fluoride concentrations of 0.04 ppm as compared to 0.02 ppm individuals (see [1] and references therein). To compare the CaF_2 particles synthesized here, with slow release fluoride devices reported in the literature, it is important to analyse their dissolution behaviour under oral conditions [3]. Furthermore it is desirable to be able to tune the fluoride release kinetics. In the literature, increased fluoride dissolution has been reported when CaF_2 particles were produced in the presence of phosphate [4]. Following the line of these results we synthesized CaF_2 particles in the presence of increasing concentrations of phosphate and compared the dissolution of pure and phosphate incorporated CaF_2. Fig. 3 shows the release of fluoride from the different particles in artificial saliva. The different CaF_2 particles dissolved fast, leading to concentrations of soluble fluoride between 0.15 ppm and 0.4 ppm within 10 minutes. This is expected to be fast enough to achieve similar fluoride levels under the conditions of constant saliva production and flow in the mouth.

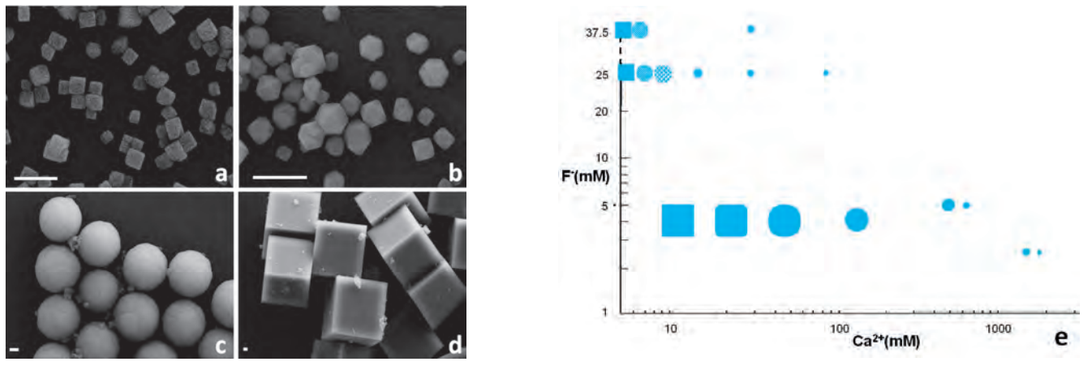

Figure 1 *Examples of fluoride particles obtained by mixing different concentrations of soluble calcium and fluoride ions (a-d) and scheme of particle shapes with respect to parent ions concentrations (e). Scalebars: 200 nm.*

Figure 2 *SEM images of CaF_2 particles adhering to tooth enamel surfaces. Scalebars: 1 µm (a, b), 0.5 µm (c).*

Conclusion and Outlook

This report describes factors which influence the morphology of CaF_2 particles and investigates their suitability as fluoride storage forms for dental care. The synthesized particles adhere to tooth enamel surfaces and can be fine-tuned to release varying levels of fluoride. Experiments are under way in order to quantify the benefit of these slow fluoride release reservoir particles on models of caries, dental erosion and re-mineralization.

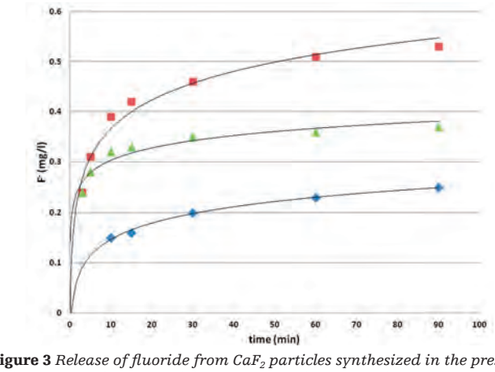

Figure 3 *Release of fluoride from CaF_2 particles synthesized in the presence of 0 mM (blue diamonds), 0.01 mM (green triangles) or 0.1 mM (red squares) phosphate.*

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Research Focus Area:
Molecular Technologies (MT)

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Funding:
Swiss Nanoscience Institute (SNI)

Economic efficiency and benefit to society:
The treatment of dental caries and erosion accounts for 5-10% of the total healthcare expenditures. The understanding and optimization of fluoride particle formation and fluoride release kinetics help to produce improved dental care formulations which benefits society. The low costs of the ingredients and the simplicity of the CaF_2 particle production process guarantee a cost-efficient realization of such improved dental care formulations.

Remineralisation of carious lesions by self-assembled peptide supramolecular networks and Hydroxylapatite nanocrystals

A tooth model was developed using synthetic nanoporous hydroxyapatite microparticles and rapid prototyping, to investigate the regeneration process of artificially induced carious lesions. Upon application of the self-assembling peptide P11 a supposed supramolecular 3D network is formed in the lesion, inducing remineralization by hydroxyapatite nanocrystals along the peptide fibrous nanostructure.

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Keywords: Self assembly; carious lesion, remineralization, peptide, hydroxyapatite, supramolecular network

Indroduction

Enormous efforts are undertaken worldwide to prevent and treat caries, but none of the provisions have proved to be effective enough [1]. Therefore the majority of all treatments still rely on the classical non-regenerative treatments exhibiting significant drawbacks and leading to further destruction of the teeth over time. In addition it has been reported that potentially harmful additives might leach out of the polymer and ceramic/polymer composite fillers [2].

At present only a few approaches have been followed and reached the market to regenerate carious lesions via re-mineralization, but with only very limited success [3]. In addition the therapeutic approaches are not suitable for regenerating carious lesions.

In 2007 Kirkham *et al* [4] proposed a new approach based on a short peptide P-11 (10 to 12 amino acids of a particular sequence) forming a 3D network by self-assembly at slightly acidic conditions (pH 6.5-7.0). The peptide diffuses in its monomeric (pH>7 salvia) form through the enamel into the dentine of the tooth. Because of the lower pH inside carious lesions, it has been proposed that the 3D network will also form inside the carious cavity indicated by first *in vitro* studies and leading to nucleation and growth of hydroxyapatite nanocrystals along the supramolecular network [5]., It was observed that small early stage carious lesions (white spots), became significantly smaller after a single topical treatment. Based on these promising results, a first generation peptide was developed and patented by the University of Leeds and further licensed to the project partner Credentis AG aiming to market and further develop this therapeutic approach.
Fig 1. Sketch (left to right); untreated lesion; application of the monomeric peptide; the hypothesized self-assembly of the peptides and remineralization by growth of hydroxyapatite nanocrystals.

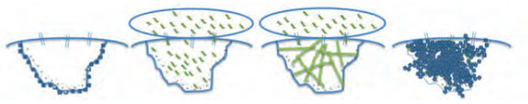

Figure 1 *Proposed mechanism of the regenerative process.*

Figure 1: First clinical trials proved to be very promising, causing amelioration of the carious lesions. The whole process and its steps are still poorly understood. At present the therapy only allows regeneration of small lesions, visible as white spots. In order to further develop the technology a deeper understanding of the whole process and its various steps, is urgently needed therefore we are aiming for the development of an *in vitro* model system, based on extracted human teeth with artificially induced caries lesions to follow the diffusion of the peptide through the enamel, the acid catalyzed supramolecular assembly of the peptide and the nucleation and growth of the hydroxyapatite nanocrystals. Because of limited availability of usable human teeth and their variability, a tailor made standardized teeth model (dense enamel layer on porous dentin) will be developed in a second phase of the project. The process is based on a rapid prototyping process (RP) using different synthetic HA (hydroxyapatite) and or ß-tricalciumphosphate materials (ß-TCP). This new approach has not been reported so far in literature. Artificial carious lesions will be introduced according to literature into both the natural tooth and the RP-based tooth model.

Results

A predictive 3D tooth model based on a RP process to investigate the effect of the peptide P11 is currently under development, Both dense hydroxyapatite and nanoporous material were synthesized by a wet-precipitation and spray drying and/or calcination process (batches >1kg/day) providing spherical particles (Fig. 2), which are suitable for the use with the rapid prototyping technology. The synthesized powders have been characterized by all means of analytical techniques.
Figure 2: First promising trials on the Z-Corp RP machine are ongoing and various binders are currently under investigation.
Carious lesions have been artificially induced by treatment of a human tooth with an acidic demineralization solution and the success of the process was analyzed by all means of analytical technologies in particular with x-ray microcomputer tomography (Fig. 3). The lesions are clearly visible (darker squares on the outer surface) in the upper rendered 3D view.
Figure 3: The carious region was subsequently treated with the peptide P11 (2 min) and then immersed in the remineralization solution (buffered saturated hyroxylapatite solution pH 7.4). The verification of the process is in progress. First results indicate a deposit of the peptide in the carious lesion. Because the identification of the protein diffusion, the network formation and detection of the remineralization inside the natural human tooth proved to be difficult, experiments have been carried out to initiate the gelation of the protein on a planar silicon wafer surface followed by the initiation of the growth of hydroxyapatite crystallites. SEM analysis revealed the formation of a 3D network and nucleation of the crystallization of HA. Another approach to prove the initial

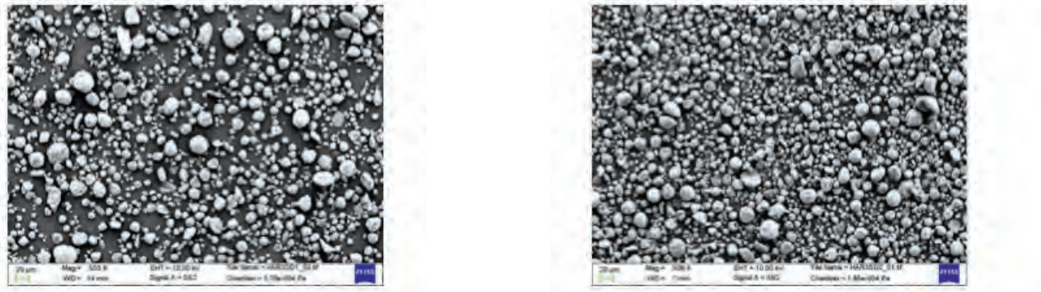

Figure 2 *SEM images of different nanoporous HA powders. Magnification approx. 500-fold, bar on bottom left corner corresponds to 20 µm.*

efficient diffusion of the peptide into the artificial carious lesions through the enamel has been followed, therefore the white spots have been treated with the peptide followed by an excision (drilling) of the carious area and subsequently analyzing the resulting powder by Maldi-TOF mass spectrometry to detect and verify the diffusion of the peptide. The mass analysis clearly gives evidence that the peptide (1598.1 D) has been diffused through the enamel into the lesion, which is one of the most critical steps of the whole process. Maldi TOF Mass spectrometry turned out to be sensitive enough to detect the small peptide quantities and will be further investigated in course of the project.

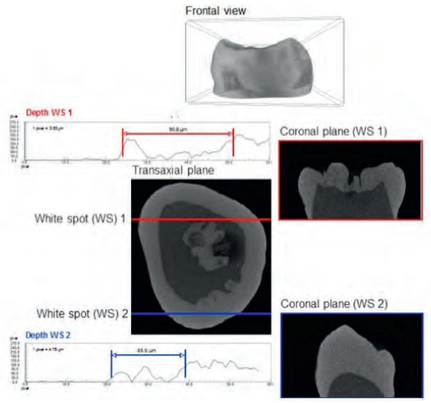

Figure 3 *Carious lesions x-ray microcomputer tomography of the treated tooth in different cross sectional views and a 3D rendered image.*

Conclusion and Outlook

Hydroxyapatite microparticles have been synthesized in the quality and amount suitable for the 3D RP process and methods to artificially induce carious lesions in human teeth have been successfully established.
Based on first promising results, indicating the deposition/network formation and growth of hydroxyapatite nanocrystals, the process will be further studied utilizing the artificial tooth model. Both fluorescently labeled and radiolabeled peptides will be synthesized and studied in order to follow the diffusion and self assembly process. In future we hope to gain better understanding of the whole remineralization process, allowing further improvement of this new therapy of early carious lesions. In a recently acquired (SNSF) follow up project, new peptides exhibiting self-assembly properties assisting the nucleation of hydroxyapatite will be developed and their properties will be studied and compared to the peptide P11.

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Research Focus Area:
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Partner:
Bert Müller (BMC Biomaterials Science Center), Michael Hug (Credentis AG)

Funding:
Swiss National Science Foundation (SNSF), Swiss Nanoscience Institute (SNI), Förderfonds Aargau, canton Aargau

Economic efficiency and benefit to society:
We report the development of an artificial tooth model for the investigation of a new approach to regenerate carious dental lesions: a self-assembling peptide is applied, forming a fibrous 3D network followed by remineralization along the 3D structure. The results will help to improve therapeutic carious treatments and to reduce health care costs significantly in the future.

Bamboo: a rich natural source of antioxidant flavonoids – Analytical technology as cornerstone for a pilot plant in China

Thorough knowledge of the flavonoid composition of bamboo species for health-related and food applications is of growing interest. The current study combines expertise from natural product research and chemical engineering and provides the basis of a pilot plant extraction unit in a bamboo forest in Fujian, China.

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School of Life Sciences FHNW

Keywords: Bamboo, flavonoids, *in-vitro* anti-oxidative properties, extraction, engineering, pilot plant

Introduction

In Europe, bamboo is mainly known as an ornamental plant, as a source for applications in the wood and fibre industry and as an energy crop. However, a growing interest in an alternative use of bamboo can be observed: this fast-growing plant provides a rich natural source of promising phytochemicals such as flavonoids. These secondary plant metabolites exhibit many beneficial physiological effects such as anti-inflammatory, anti-oxidant, anti-viral and anti-ageing properties or prevention of cardio vascular diseases [1, 2]. Despite this, there is still a lack of information on the secondary metabolites responsible that are present in the many different bamboo species around the world. Thus there is a great need for fully characterized and controlled bamboo extracts for therapeutic, cosmetic and beverage applications.

In this research project, the qualitative and quantitative chemical composition of the leaves of 24 morphologically heterogeneous bamboo species were determined by high performance liquid chromatography mass spectrometry (HPLC-MS), with a focus on flavonoids. The 24 species, belonging to the three different bamboo genera, *Phyllostachys*, *Fargesia* and *Sasa*, originate from a Swiss organic bamboo forest close to Waldkirch (SG).

In addition, extraction of leaf material was optimized on a pilot plant scale; application of high-end analytical technologies for exact characterization of the plant material gains great synergy in combination with process technology. On the basis of the combination of those disciplines, appropriate selection of bamboo species and a tailored process for a pilot plant extraction unit was achieved.

Results of analytical investigations

One desired criterion for utilization of bamboo as a therapeutic crop is a naturally high content of total flavonoids. This property might be influenced by genus, species, age or geographic origin of the plant. Extraction yield (in % of dry weight leaves) and total flavonoid content served as read out for the evaluation and differentiation of bamboo species. Classical natural product extraction procedures such as maceration, digestion, soxhlet, microwave and solvent extraction were assessed to find the most efficient and economical process. Tight feed-back loops between process engineering and analytical technologies were established and allowed a thorough evaluation of the process from the outset. However, it is not only the total flavonoid content that determines the assets of a species but also the individual flavonoid composition.

Type	Phyllostachys (n=15)	Fargesia murielae (n=8)	Sasa (n=1)
Extraction yield [% dry weight]	20.7%	22.2%	17.4%
Orientin [mg/kg leaves]	426.1	4.2	nd
Isoorientin [mg/kg leaves]	5317.2	3991.9	1099.3
Rutin [mg/kg leaves]	113.5	nd	nd
Isovitexin [mg/kg leaves]	213.5	37.7	10.5
Luteolin [mg/kg leaves]	8.6	12.8	nd
Kampferol [mg/kg leaves]	19.2	24.9	13.2
Tricin [mg/kg leaves]	76.8	106.8	434.5
Vitexin [mg/kg leaves]	34.6	nd	nd
Total flavonoid [mg/kg leaves]	5744.4	4155.1	1557.5
ORAC TE umol/g Extrakt	11432.4	11060.2	12478.0

Figure 1 *Flavonoids determined by LC-MS/MS in Swiss bamboo*

Robust liquid chromatography (LC) tandem mass spectrometry (MS/MS) analysis allowed for flavonoid characterization and quantification. Based on retention time and MS/MS fragments, the flavonoids Orientin, Isoorientin, Vitexin, Isovitexin, Rutin, Luteolin, Kaempferol and Tricin were identified and quantified as major components. Myricetin, Quercetin, Catechin hydrate, trans-p-Coumaric acid, Caffeic acid and Gallic acid were also identified. The resulting average concentrations for the three different bamboo genera obtained by triplicate determination (in mg substance per kg leaf) are depicted in figure 1. Different bamboo species can be clearly distinguished by an altered flavonoid profile. In addition, different bamboo genera show characteristic patterns of individual flavonoids. *Phyllostachys* bamboo generally exhibits both higher total and higher individual flavonoid levels compared to *Fargesia* and *Sasa* (Fig. 1). Tricin is most prominently found in *Sasa* bamboo.

Anti-oxidative capacity was tested for all bamboo species by assessing the anti-oxidative capacity (ORAC) [3]. It was shown that all bamboo species exert potent antioxidant effects *in vitro* (Fig. 1). From the results mentioned above it is obvious that bamboo is an important source of antioxidant compounds and therefore represents an interesting raw material for further development of bamboo-derived food, beverage additives, supplements or cosmetic formulations. Principal component analysis, based on flavonoid levels for the 24 different bamboo species, clearly reveals similarities within a genus and differences in between the genera as illustrated in figure 2.

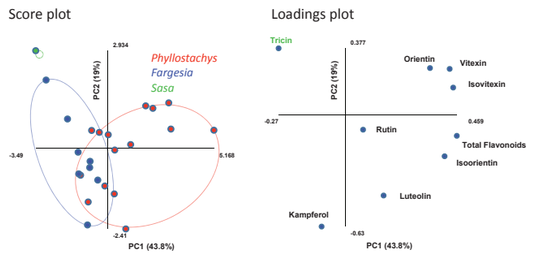

Figure 2 *Principal Component Analysis of Swiss bamboo reveal similarities within genera*

Results on process engineering

Process engineering of the technical bamboo leaf extraction was a two-step approach: First, in a basic engineering phase, the main focus was to find environmentally friendly process parameters which allow for a maximum yield of flavonoids with a minimum amount of solvent and energy. The next step was to find equipment which fits these requirements and to design the process chain from the delivery of leaf material, via spray-dried extracts to waste disposal.

The basic engineering phase started with the choice of an appropriate flavonoid solvent. In lab extraction almost every solvent, including harmful and highly flammable ones, can be used to extract target components with a high yield and selectivity. However the technical extraction of herbal material is affected by restrictions on the class of solvents (e.g. explosion proof requirements, solvent recovery and waste management). Hence, only a few solvents can be considered for production scale. It was demonstrated by analytical investigations that polar solvents like ethanol, methanol and water can easily extract a reasonable amount of flavonoids. However, water was used for the pilot technical extraction due to its non-critical properties and good availability. In the next step the optimal process parameters for extraction with water were investigated. The focus here was on extraction temperature, amount of total solvent, material pre-treatment and specific parameters (such as stirring rate, hold-up etc.). It could be shown that with a temperature close to the boiling point of water at ambient pressure, maximum flavonoid yield (=0.7% based on Isoorientin) could be achieved. However, with moderate temperatures (e.g. 60°C), a sufficiently high amount of Isoorientin could also be extracted.

It was surprising that a maximum extraction rate could be achieved with a simple pre-cutting of the leaf material. Neither milling of the plant material nor extraction of the untreated leaves led to a better extraction result.

With these promising results a concept for a 100 kg/hour extraction plant in China was engineered. Besides the required footprints for the technical equipment, material and personnel flow were taken into account, not to mention room for shipment of raw material and waste disposal on the basis of 40 foot containers. Currently, based on a 3-D model generated to visualize the proposed plant layout (Fig. 3) a pilot plant is build up in Fujian, China. Present work concentrates on further energy savings, as well as higher yield and throughput of the planned extraction plant.

Conclusion and Outlook

A robust LC-MS/MS method was developed for quantification of individual flavonoids in bamboo leaf extracts that allows a detailed selection of the best suited species. All bamboo genera reveal high radical scavenging properties. Principal component analysis allows the straightforward differentiation between bamboo species. Further studies on other beneficial physiological effects of bamboo are currently under investigation in our labs.

Based on the very high level of analytical information, basic engineering for a technical bamboo leaf extraction plant could be carried out. Supported by pilot plant trials in the chemical engineering test facility in Muttenz, the design of apparatus and of a complete environmentally-friendly extraction plant could be generated. Based on this information, the customer's project has entered the realization phase.

Figure 3 *3-D model of extraction pilot plant in Fujian, China*

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Research Focus Area:
Molecular Technologies (MT)

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Partner
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Funding
Organic Bamboo Industries AG

Economic efficiency and benefit to society

On basis of these investigations, beneficial health effects of flavonoids can be easily exploited from bulk biomass. Bamboo leaves, a so far unused natural by-product turns into a renewable source for valuable natural products. An environmentally sustainable process for the use of bamboo has been developed from thorough analytical chemical analysis to pilot plant design. It is now in the realisation phase.

Cyclodextrin-based polymers: efficient binders of pharmaceuticals in water

In a world facing water scarcity, the presence of pharmaceuticals in water represents serious environmental and human health issues. In the present project, we are working to develop new polymeric materials for the detection of pharmaceuticals in water.

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School of Life Sciences FHNW

Keywords: Polymers, cyclodextrins, pharmaceuticals, water

Introduction

In the last decades, the presence of pharmaceuticals has been reported in the water cycle, including surface water, wastewater, groundwater and drinking water. We are working on the development of synthetic materials that can be used for the detecting and removal of those pharmaceuticals from water.

The production of synthetic materials possessing specific molecular recognition properties is a continuous challenge, with a wide range of industrial applications including biomedical, pharmaceutical and environmental, as well as separation techniques, to name but a few. In the 1980s molecular imprinting came to the fore as a versatile technique for the production of polymers with enhanced molecular recognition properties. It is based on the polymerization of functional monomers with crosslinkers in the presence of a template molecule (i.e. target). The functional monomers interact with the template to form a supramolecular complex before the cross-linking reaction. After polymerization, the template is removed to yield recognition sites complementary to the template structure. While a vast number of reports have been published on molecularly imprinted polymers (MIPs), their commercial use is still limited. The inherent constraint of MIPs is their relative high production costs, due partly to the cost of the starting building blocks but mainly to the difficulty of removing the template from the MIP at the completion of the synthesis.

We have recently developed a series of polymeric systems, via template-free approaches, which possess enhanced molecular recognition properties for pharmaceuticals in water. Those polymers are produced using monomers based on cyclodextrins with an inherent affinity for the target molecules.

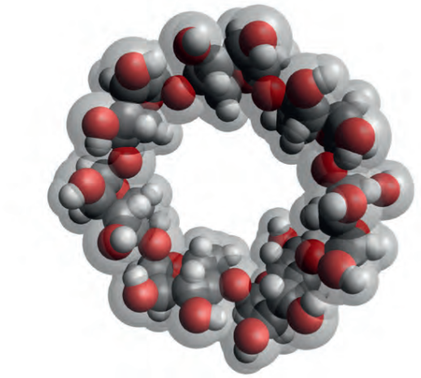

Figure 1 *A cyclodextrin macrocycle (top view)*

Cyclodextrins are cyclic oligomers composed of 6, 7 or 8 D-glucopyranosidic units, for α, β and γ cyclodextrins, respectively; cf. Fig. 1 [1] They are bound via α-(1,4) glucosydic linkage and are produced by the enzymatic degradation of starch by cyclodextrin glycosyltransferase, an α-amylase found in several micro-organisms (e.g. *Bacillus circulans*, *Bacillus macerans*, *Bacillus stearothermophilus*). Cyclodextrins are widely used for pharmaceutical formulation because of their known ability to include hydrophobic drugs inside their macrocyclic cavity.

The polymers we produced (cyclodextrin-based polymers or CDPs) are tested both for applications as recognition elements in an environmental diagnostic tool and as removal/recovery material for biotechnological or environmental applications.

Results

We have developed two different approaches for the high-throughput production of a series of cyclodextrin-based polymers (CDPs). The first approach is based on the photo-catalyzed reaction of a cyclodextrin derivative with additional monomers and cross-linkers (cf. Fig. 2) [2]. The synthesis was carried out in a multiwell plate using an acryloyl β-cyclodextrin and 1-hydroxycyclohexyl phenyl ketone as an initiator. A number of additional monomers (acrylamide, N-isopropylacrylamide, 2-hydroxyethyl methacrylate, 2-vinylpyridine, acrylic acid, itaconic acid, and 2-acrylamido-2-methyl-1-propanesulfonic acid) and cross-linkers (divinylbenzene, ethylene glycol dimethacrylate, and trimethylolpropane trimethacrylate) were added to the formulation at different molar ratios; cf. Fig. 2. The binding properties of the produced polymers of a mixture of molecules of interest (acetaminophenol, atenolol, caffeine, ofloxacin, ciprofloxacin, tetracycline, sulfamethoxazole, chloramphenicol, (±)-propranolol, and diclofenac) were assayed in water using an HPLC-based method. It was demonstrated that the binding properties of the produced polymers could be tuned by varying the monomers used for the synthesis. Two polymers were selected and produced in the multigram quantity. It was demonstrated that the larger reaction scale did not disturb the polymerization reaction and that the produced polymers retain their molecular recognition properties.

The second approach is based on the reaction of three different cyclodextrins, namely α-, β- and γ-cyclodextrin, four different diisocyanate crosslinkers (1,4-phenylene diisocyanate, toluene 2,4-diisocyanate, isophorone diisocyanate, and hexamethylene diisocyanate), and four different carboxyl-containing dihydroxy monomers (2,2-bis(hydroxymethyl)propionic acid, 2,5-dihydroxybenzoic acid, 2,5-dihydroxyterephthalic

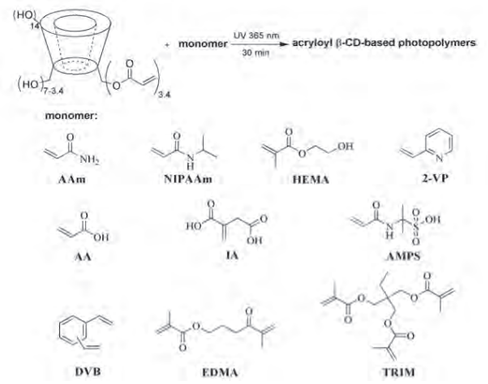

Figure 2 *Synthetic route to cyclodextrin-based photopolymers and chemical formulas of the monomers used for the synthesis*

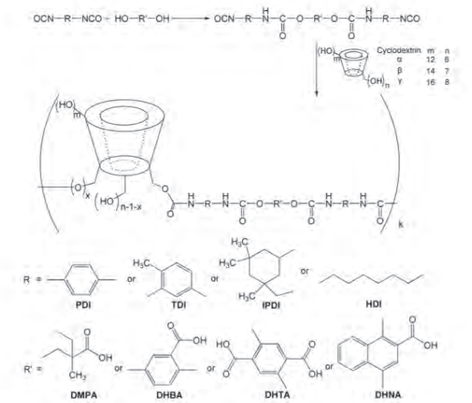

Figure 3 *Synthetic route to cyclodextrin-based polyurethanes and chemical formulas of the monomers used for the synthesis.*

acid, and 1,4-dihydroxy-2-naphthoic acid). It allowed the production of 51 different polyurethanes that were assayed for their ability to complex drugs [3]. In addition to the enhancement of the recognition properties of the CDPs produced, this method allows the direct use of native cyclodextrins; that may be crucial for decreasing the production costs of the CDPs and thus facilitating their industrial application.

The synthetic methods developed allowed the development of polymers specific for a series of pharmaceuticals of interest including diclofenac, sulfamethoxazole and levofloxacin [4].

Conclusion and Outlook

We have developed a new approach to producing polymers with specific molecular recognition properties for pharmaceuticals. It was demonstrated that this method allows the production of polymers with enhanced molecular recognition of a series of pharmaceuticals in water.

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Research Focus Area:
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Partner:
Yves Dudal (INOFEA GmbH)

Funding:
Co-financed by Commission for Technology and Innovation (CTI)

Economic efficiency and benefit to society:
Benefit to society is foreseen in terms of new and efficient available products to detect and remove pharmaceuticals from water. From an economic point of view, the present technology will be commercialized by INOFEA and is expected to contribute to the creation of new jobs.

Recombinant Immunoglobulins for Autoimmune Medical Diagnostics

Autoimmune diseases are most challenging for current medical diagnostics. These diseases arise through mechanisms of compromised immune self-tolerance, commonly through autoantibodies recognizing self-antigens. This report outlines the development of recombinant disease-state specific autoantibodies for application in one a autoimmune diagnostic.

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Keywords: diagnostics, recombinant proteins, antibodies, autoimmune disease

Introduction

Autoimmune diseases are associated with loss of immunological tolerance, which is the normal ability of an individual to ignore endogenous "self" pathogens, while still reacting to "non-self" pathogens. Autoimmune breakage leads to the immune system's mounting a detrimental and specific immune response against self-determinants, giving rise to a spectrum of disease states.

Guillain-Barré syndrome is one acute autoimmune polyneuropathy, a disorder affecting the peripheral nervous system. The clinical relevance of the ganglioside autoantibodies (gangliosides are "self") to contribute directly to the pathogenesis of these peripheral neuropathies is well established [1]. For applied diagnostics, the detection of anti-ganglioside autoantibodies in patients is vital; usually these are of the IgM antibody isotype and are associated with multifocal motor neuropathy and lower motor neuropathy, clinically characterized later-stage by muscle weakness and atrophy. Polyclonal antibodies of IgG isotype may also be detected in certain patients.

Gangliosides are acidic glycosphingolipids localized in the outer layer of plasma membranes and abundant in the myelin sheath of Schwann cells of peripheral nerves. Ganglioside M1 (GM1) is the most abundant ganglioside; it has important physiological properties and affects neuronal plasticity and repair. Gangliosides are long-chain aliphatic ceramides linked to 2 or more hydrophilic sugars and 1 to 4 sialic acid residues (N-acetylneuramic acid) (Fig. 1). The surface displayed sugars are thought to be the autoimmune targets.

The causal disease mechanism appears to be "molecular mimicry", where exogenous antigens share sufficient structural similarity with host antigens to lead to the cross-activation of autoreactive T or B cells. Infection through *Campylobacter jejuni* is the proposed triggering event for anti-GM1 neuropathy [2]. Strain-specific lipopolysaccharide expression (bacterial LPS) presents near perfect overlap with the structure of the endogenous GM1 sugar.

Since autoantibodies are a major diagnostic marker for this disease class, it is the goal of this project to produce disease-state specific recombinant autoantibodies for the development of improved diagnostics.

Results

The first R&D phase was the generation of recombinant antibodies for both human IgG and IgM isotypes with variable-region binding specificity against the target antigen GM1. IgG isotype antibodies consist of paired heavy-chain domains complexed with paired light-chain domains, with the two variable region antigen-binding domains shown schematically in red (Fig. 2). The human IgM molecule is a large complex glycosylated disulfide-bond protein consisting of a pentameric repeat imparting on the antibody an antigen binding valency of ten. The antigen specificity of the variable regions grafted onto both the recombinant IgG and IgM constant regions are identical i.e. anti-GM1.

The molecular cloning of the heavy and light chain variable antibody genes was achieved from GeneBank sequences corresponding to disease-state specific antibody expressing immortalized human B cell lymphoblasts. The antibody genes were cloned into specially designed expression vectors to direct subsequent protein production.

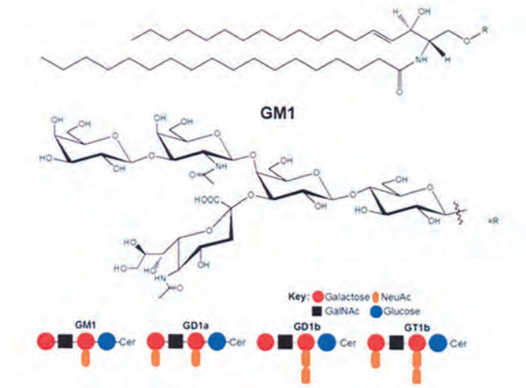


Figure 1 *Structure of the ganglioside autoantigen GM1 present on the surface of peripheral nerve cells*

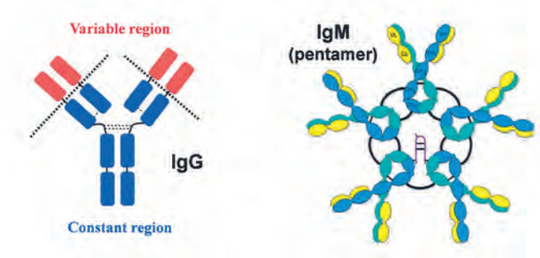
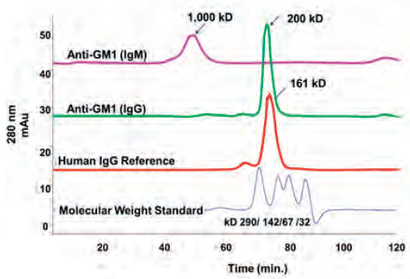


Figure 2 *Schematic of human antibodies of the isotypes IgG and IgM*

The recombinant antibodies were produced by the technology of transient gene expression in mammalian suspension CHO cell culture. The production phase lasts from 2-10 days until the proteins are ready to harvest. Recently scientists in biotechnology have started to replace traditional stainless steel bioreactors with single-use systems in order to increase process efficiency, with the advantages of avoiding tedious cleaning and re-sterilization, controlled contamination risks as well as short set-up times and installation [3]. This project used the Millipore CellReady 2.4 Liter disposable bioreactor.



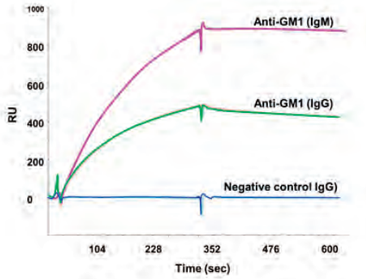


Figure 3 *Analysis of recombinant anti-GM1 antibodies of isotypes IgG and IgM by native size-exclusion chromatography (left) and Biacore real-time molecular interactions (right)*

The recombinant antibodies were characterized *in vitro* using the bioanalytical methods of capillary electrophoresis, analytical size-exclusion HPLC and target binding analysis using Biacore (Fig. 3). On size-exclusion chromatography the recombinant IgM and IgG showed relative molecular masses of approximately 1,000 and 200 kilodalton (kD) respectively, consistent with their native structure. To characterize antibody-antigen interactions Biacore was used, a surface plasmon resonance based biosensor that determines active concentrations and characterizes molecular interactions in terms of both affinity and binding kinetics. On-phase binding (strong up-slope) and off-phase release (weak down-slope) are shown. The recombinant IgM and IgG show dissociation constants (KD), defined as an equilibrium constant measuring propensity of the antibody to separate (dissociate) from its GM1 target, as approximately 30 pM and 1 nM, respectively. The higher KD for the IgM recombinant antibody, despite it having the identical variable binding domains as the IgG, is consistent with its higher pentameric structural valency which confers greater avidity.

Specificity of the antibodies for ganglioside GM1 was measured by Enzyme-linked immunosorbent assay (ELISA) using microtiter plate positive and negative samples of six related gangliosides (GM1, GD1b, GQ1b, GD1a, GM2, GA). The recombinant antibodies were shown to specifically bind only GM1. In the anti-ganglioside antibody kit format, gangliosides are precoated on microtiter plates, incubated with patient serum and subsequently detected using secondary antibody binding followed by an enzyme label reaction. Technical issues uncovered during this project included the notably unexpected instability of anti-GM1 IgG and difficulties in IgM purification. One separate target we originally planned was also the anti-MAG autoantibody (myelin-associated glycoprotein), remaining work uncompleted.

Conclusions and Outlook

Our investigations showed that specific recombinant antibodies of IgM and IgG isotypes can be generated with GM1 autoantigen specificity. Moreover, these enabling technologies should further extend the discovery, characterization and standardization of autoantibodies for other challenging autoimmune diseases. Diagnostics for autoimmune diseases represent a fast-growing area. These diagnostics help the clinical physician in the testing of parameters relevant to the diagnoses of these disease states, for comparative or progressive diagnosis or for determining the therapeutic effectiveness of treatment or relapse.

The commercial advantages of human-similar recombinant proteins over the use of patient derived sera are manifold; the material is homogeneous, well characterized, reproducible and potentially available in unlimited supply. It is also not associated with any legal, ethical or safety issues surrounding the use of human derived material. In the future such diagnostic reagents might serve as gold standard reference materials for international quality circles and regulatory authorities [4, 5].

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Research Focus Area:
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Economic efficacy and benefits to society:
Diagnostics which better serve the health care practitioner provide significant impetus, both economically for the manufacturer and for advancing the effectiveness and safety of the health care process. New molecular technologies are driving many of these advances.

Meso scale technology: an effective tool for the development of multiplex immunoassays

Immunoassays, and especially Enzyme-linked Immunosorbent Assays (ELISA), are bioanalytical tools of proven accuracy and robustness for a variety of applications. Meso scale technology confers valuable additional features in terms of dynamic range and multiplex promising a new age of immunodetection.

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Keywords: Electroluminescence, immunoassay, meso scale, preclinical studies, multiplex, dynamic range

Introduction

Multiplex assays enable the simultaneous detection of several biomarkers in a unique sample. In basic research, multiplexing technologies for instance micro-arrays, are already effectively implemented. The methods target thousands of different molecules and provide impressive screening capacity generating significant amounts of investigative data. The bionanalyst, as an application scientist, pursues more practical purposes. He is indeed demanding for procedures enabling simultaneous detection of multiple targets in a single sample, but he necessarily favors accuracy over multiplicity. He might consider multiplexing only in the case that 1) the same or better accuracy than the acknowledged single marker method is achieved and 2) the application confers an objective practical advantage in terms of time or costs. Despite constant industrial and research innovation efforts in this direction, the multiplex method of proven utility may today still be considered as a rarity in the eyes of a bioanalyst.

The meso scale technology provided by Meso Scale Discovery allows the simultaneous analysis of multiple biomarkers. The MSD system combines in a very simple and elegant manner micro-array technology and ELISA. Each well of the microtiter plate is organized like a micro-array (chess-board). Discrete areas of the well are spotted with four to ten capture antibodies. There are two architectures to run an assay. Either the biomarker captured by the antibody will further be tied to a ruthenium-chelate labeled detection antibody (sandwich assay) or unoccupied biomarker binding sites on the capture antibody are saturated with the ruthenium-chelate biomarker conjugate (competitive assay; Fig. 1b). The ruthenium-chelate label used emits light at 620 nm which is detected by a CCD camera (Fig. 1d). The generation of the signal is mediated by an effective signal transduction system based on electrochemiluminescence. The signal transduction system allows for repeated cycles and thus the amplification of the signal (Fig. 1a). A four-parameter weighted logistic fit curve is generated to gather sample concentrations using the Discovery Workbench 3.0 software (MSD).

Harlan Switzerland as industry partner and the bioanalytics group of the School of Life Sciences as University partner started an 18-months project under the premises of CTIs special innovation programme “Starker Franken”. Harlan Switzerland provides worldwide pharmaceutical, agronomic and chemical companies with toxicology and ELISA based analytical studies for product registration purposes. Harlan has an exhaustive and acknowledged expertise in the field of preclinical studies and leads its own research on biomarker development. The purpose of its collaboration with the School of Life Sciences aims at investigating the implementation of current Harlan ELISA procedures to meso scale technology.

The provider of the meso scale technology, MSD, offers an extended portfolio of "ready-to-use" biomarker multiplex assays. These assays generally fit the state-of-the-art in terms of bionanalytic application in pre-clinical studies. Nevertheless, each expert customer may have specific requirements and wish to have test panels proposed in different combinations or configurations. Consequently, Meso Scale Discovery also proposes tools and services enabling the customization of its multiplex assays, consisting primarily of labeling or labeled molecules and multiplex spot printing.

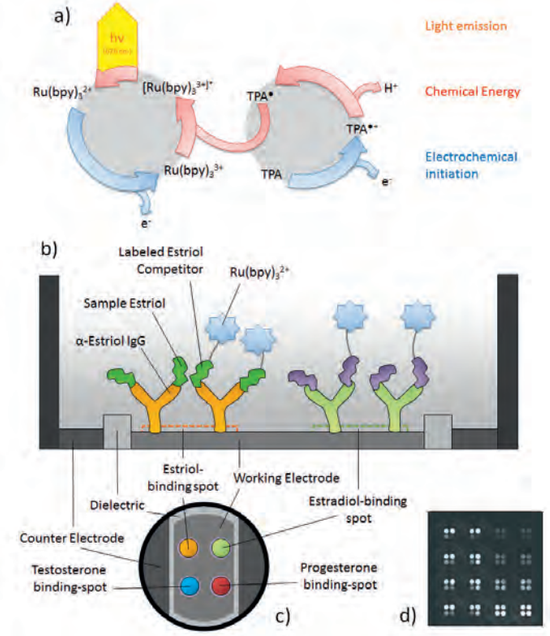

Figure 1 *Principles of an electrochemiluminescent immunoassay according to the manufacturer [1]. In this schema estriol represents one biomarker of a steroid hormone 4-plex competition assay. a) An electric impulse induces the electrochemical energy transfer from tripropylamine (TPA) to tris-bipyridine ruthenium II (Ru(bpy)32+) resulting in light emission. b) Ru(bpy)32+ constitutes the core part of the label tagging the competitor molecules. These molecules compete with the sample estriol for the binding to specific capture antibodies (anti-α-estriol IgG) immobilized on the well bottom. c) The well bottom contains a set of electrodes. The capture antibody for each marker is spotted separately. d) The picture represents a typical intermediate output. The MSD device quantifies the light emission of each spot.*

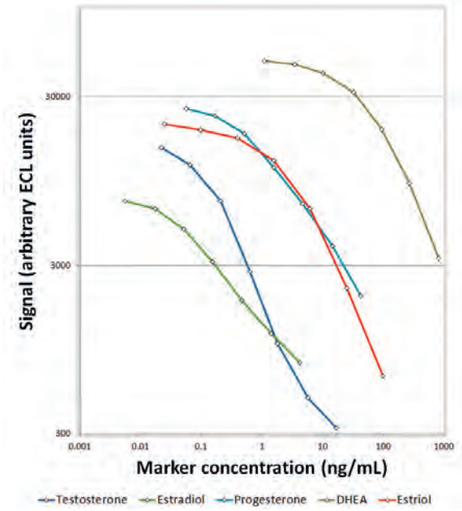

Figure 2 *The standard curve of the estriol singlet assay (Est) is compared to the standard curves of the rat inflammation panel 1 assay (testosterone, estradiol, progesterone and DHEA), as published by the manufacturer [2]. The graph illustrates the broad dynamic range from 0.001 to 300 ng/mL marker concentration.*

Results

The focus of the CTI project is not on evaluating the meso scale technology, but rather seeks to assess the technical and practical feasibility of reconfigured multiplex assays. The tailored configuration allows the analysis of a set of biomarkers dedicated to support toxicological studies of drug candidates according the client's demand.

In the course of the CTI project, three novel multiplex assays will be developed. As an example we reconfigured the commercial steroid hormone panel 4-plex, which allows the analysis of estradiol, progesterone, testosterone & DHEA by replacing DHEA with estriol. In a first step we have screened several anti-estriol antibodies and selected an antibody which showed an optimal binding performance. Because of the low molecular mass of the biomarkers, the architecture of the assay requires a competition mode (Fig. 1b). Consequently, a conjugate of estriol coupled to ruthenium-chelate was synthesized. Thereafter, the assay was set up and optimized by varying the concentration of involved reagents (Fig. 2). We demonstrated that the assay delivers the necessary sensitivity. The assay is specific as confirmed by the absence of cross-reactivity with the three other markers of the multiplex. Simultaneously we already developed a nephrotoxicity 6-plex in the same manner.

Extending these technical issues concerned with development, optimization and validation of a set of multiplex tox assays, the project also treats aspects of regulatory nature. Particularly the whole process of validation has to be carried out in a GLP-regulated environment. Therefore we are in the process of establishing a laboratory which conforms to GLP regulations. Collaborators involved in the project will be trained in accordance to Harlan's quality management system. This endeavor represents an exceptional achievement for the School of Life Sciences.

Conclusion and Outlook

The meso scale technology provides significant improvements in comparison to ELISAs and other conventional immunoassays [3]. The slightly better sensitivity is one of them and not even necessarily the most important. Due to electric excitation and a specific emission range, signal-bound interferences are considerably reduced. At the same time, the dynamic analytical range covers almost five logs, while conventional methods generally only cover two. This broad dynamic range considerably facilitates the development of an immunoassay multiplex since it enables the combination of single assays with strongly differing signal ranges (Figure 2). Furthermore the broad dynamic range will contribute to the reduction of the workload in routine analytics. The reagent costs are approximately 2 CHF per biomarker. A full plate with up to 96 tox samples multiplexed with 4 biomarkers per well will cost around 1’000 CHF.

In the near future, developed assays will be produced by MSD and be involved in Harlan pre-clinical studies. At this point, they will reveal their economic utility, which is predicted to be high [4]. The innovative immunoassay technology should increase capacity and reduce costs. It is also expected to widen the application field of Harlan's activities, for example enabling multimarker studies in small animals (mouse, rat) where sample volumes represent a critical issue.

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Co-financed by Commission for Technology and Innovation (CTI)
Economic efficiency and benefit to society:
Harlan Switzerland provides worldwide pharmaceutical, agronomic and chemical companies with toxicology and ELISA based analytical studies for product registration purposes. The transfer of Harlan ELISA activities to Meso Scale technology would rapidly widen its application field, increase its capacity and reduce costs.

De-alcoholisation of beer using membrane technology

Non-alcoholic beer is becoming more and more a lifestyle soft drink, especially if the typical "beery" flavor can be maintained during the de-alcoholisation process. Here a compact membrane device is described which allows the production of 50 hl of alcohol-free beer – with a great taste.

Wolfgang Riedl
School of Life Sciences FHNW

Keywords: De-alcoholisation, beer, membrane technology, refractometer

Introduction

The demand for non-alcoholic beer has grown steadily in recent years, which means that even small- and medium-size breweries are faced with the question of how to serve this market. Once a brewery has decided to enter the non-alcoholic market, it must find appropriate technologies that meet its specific requirements in terms of robustness, staffing and adaptability within a given space. In many cases, classical thermal treatment to remove alcohol from water is applied [1]. However Nanofiltration membrane technology could be used for this application, due to its being non-thermal and kind to aroma and taste components. During this project, a compact unit for the de-alcoholisation of up to 50 hl/day should be developed with the focus on using the best available membrane and robust process conditions [2].

Results

Nanofiltration is described as a technology which is kind to aroma compounds during de-alcoholisation of beer since no thermal treatment is required, as opposed to distillation. The special structure of the membrane impedes passage of molecules with a greater molecular weight than 100–300 g/mol, corresponding to the weight of most of the aroma compounds responsible for the typical beer taste. Hence, only lower molecular-weight compounds such as water and alcohol can pass through the membrane to the so called permeate side. However, when removing alcohol from beer by means of membranes, not only alcohol passes through the membrane but also water and a few beer aroma compounds. In a batch mode operation this leads to an aroma concentrate anyway, reduced in both the alcohol and water content. In order to generate an alcohol free beer, which generally corresponds to a maximum alcohol content of <0.5 vol.%, the concentrate has to be re-thinned with pure water to the original starting volume. This water needs to be degassed to prevent any oxidative deterioration of the beer's flavours. The degassing step can also be done with membrane technology, which is part of another research project.

Today, the market offers a broad range of different membranes with different separation characteristics. Hence, for designing a membrane-driven de-alcoholisation process for a brewery a screening is required which involves the parallel testing of multiple membranes to decide which are most useful and appropriate for the desired separation task. In this study, ten different membranes were screened in total and several membranes were eliminated in advance because of their specific separation characteristics, published by the suppliers.

The key criterion for the screening evaluation was the separation of alcohol but also a high retention rate to prevent beer aroma components from being lost from the original beer. In addition, a sufficiently high amount of removed alcohol/water per square meter of installed membrane area (="flux") is required in order to give the membrane unit a small footprint.

The specific membrane characteristic to separate ethanol prior to water is expressed by the selectivity factor S, whereby S is defined as the ratio between two compounds in the initial solution (=beer) and the permeate.

$$S_{ij} = \frac{W_{i,P} / W_{j,P}}{W_{i,F} / W_{j,F}}$$

whereby:
i,j = compounds
P = permeate
F = feed
W = weight fraction

Since the removal of alcohol from beer is the main focus of the process, a selectivity-factor greater than 1 is required; otherwise ethanol would be concentrated in the beer.

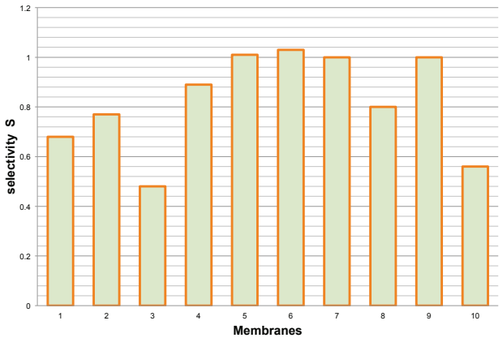

Figure 1 *Selectivity for different membranes*

In figure 1 the results of the membrane comparison are shown. It can be seen that only four out of ten membranes have a selectivity factor greater than 1, making them interesting for further studies. The selectivity of the other six membranes was in the range of 0.5 – 0.9. Even though those membranes are not suited for the de-alcoholisation, the results are interesting anyway: it allows the use of these membranes for spirit-making with high content of alcohol and aroma. The distillation can be stopped at lower alcohol content and with a membrane concentration step afterwards the desired end concentrations can be obtained at gentle since non-thermal conditions to the aroma.

Of the four membranes with a selectivity >1, however, only two membranes (no.s 5 and 9) had a sufficiently high flux. Hence, for the on-going design of a compact de-alcoholisation skid-mounted unit, only these two membranes were used. It needs to be mentioned that with each of the membranes tested, permeates were clear and colorless, which indicates that only a small quantity of beer components enters the permeate. However the familiar ethanol smell could be found in every permeate. Comprehensive GC analysis confirmed these impressions.

The absence of color in the permeate allowed for the use of an online refractometer to measure the alcohol concentration in the permeate. In general, refractometry allows for the determination of a compound in a binary solution, whereby the deflection angle of a light beam (=refraction) serves as the direct measure of the concentration of the target component. In beer, which is a multi-component mixture of several hundred substances, this technique fails because the refractive index cannot be associated with any particular component. Using a membrane with a well described separation characteristic and selectivity, the installation of a refractometer on the permeate side allows the generation of information about the actual alcohol concentration in beer. This is required for the definition of stop criteria for the de-alcoholisation process.

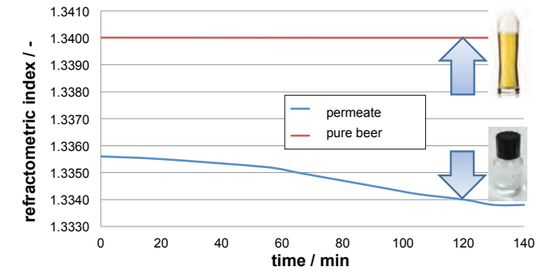

Figure 2 *Refractometric index as function of ethanol content in binary and multi-component mixture (beer)*

Since the refractometric index of beer and permeate differ so much, it can also be used as a control mechanism for the stability of the membrane. In the event of a membrane failure, beer enters the permeate side unhindered and will be detected immediately by the refractometer (see Fig. 2). The refractometer features a programmable turn-off function that is triggered when the inspected solution reaches certain threshold values (e.g. refractometric index of pure beer). Since it is directly linked to a regulation system, the membrane unit turns itself off automatically and reverts to a safe sleep mode.

Using a screened membrane for the separation of alcohol and a refractometer for online measurement and controlling, the industrial partner could plan and erect a compact skid mounted unit (see Fig. 3) which enables particularly mid-scale breweries to use an innovative technology for the generation of alcohol-free beer. This unit was presented to the public at the international fair "brau beviale" 2011 in Nuremberg, Germany.

Conclusion and Outlook

The joint project between a commercial enterprise and the School of Life Sciences shows that knowledge of membrane technology can be combined with robust design and functionality to generate an interesting, compact system. This skid-mounted unit saves space, is easy to operate, and requires no special knowledge to use correctly. This makes this innovative technology for removal of alcohol from beer easily accessible, especially for small- and medium-size breweries [3].

Figure 3 *Skid mounted nanofiltration unit for de-alcoholisation of 50 hl/d beer*

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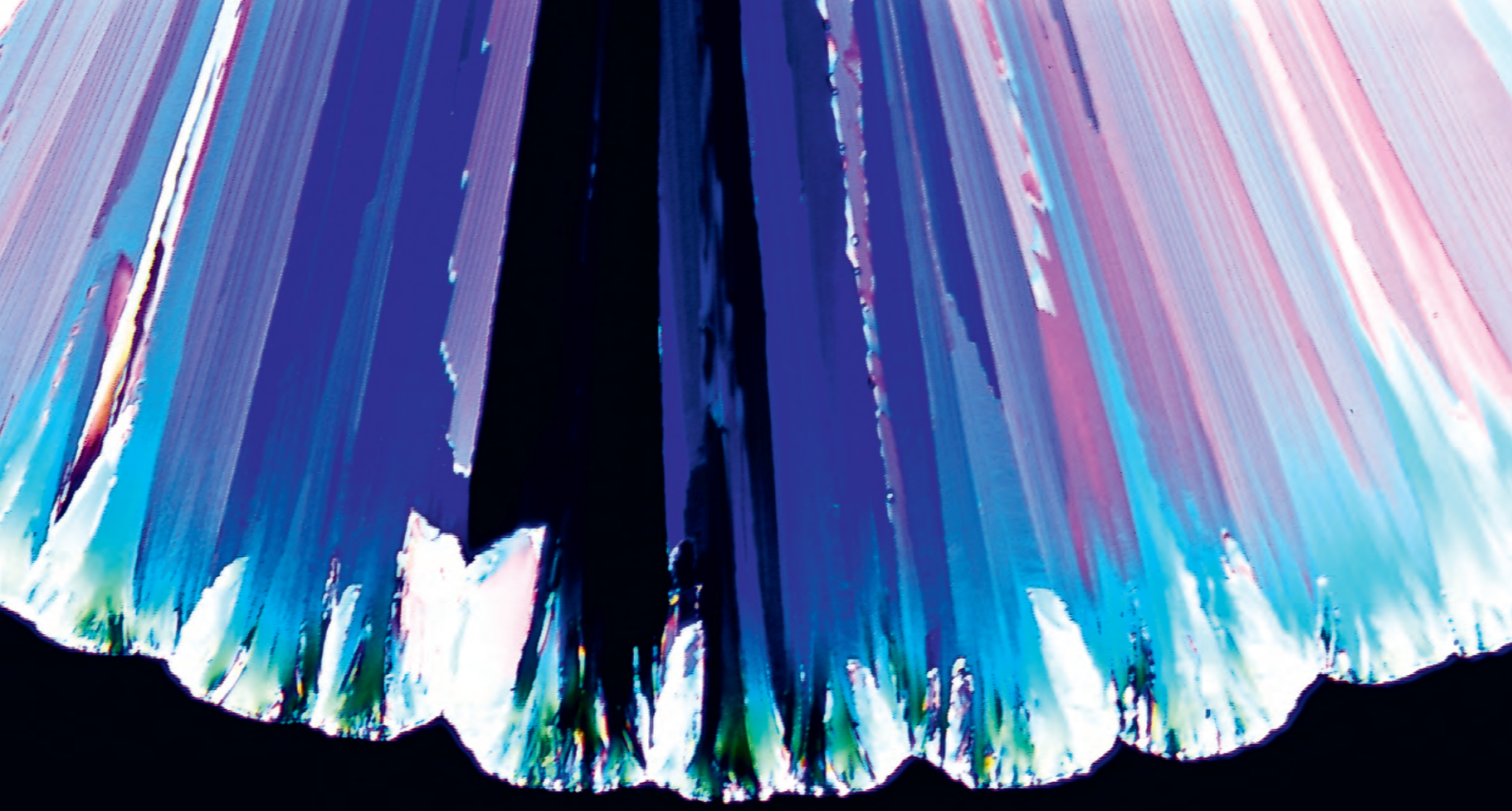
Rudolf Graf (Anlagenbau AG)
Funding:
Anlagenbau AG

Economic efficiency and benefit to society:
Nanofiltration for the de-alcoholisation of beer maintains the typical beer aroma. Due to its operation at ambient conditions it reduces both the required thermal energy and product stress and represents a true commercial alternative for breweries.



Therapeutic Technologies (TT)
Technologies for the development and production of pharmaceutical, biomedical products and therapeutic systems

Synthesis and study of silica nanoparticles grafted with biocompatible polymers and loaded with Indocyanine green

Hybrid nanoparticles consisting of the combination of an inorganic silica core and a biodegradable polymeric shell are used for the stable encapsulation of the light and highly water sensitive dye indocyanine green, allowing applications in a body fluid environment. The dye is protected by encapsulating it in the biodegradable polymeric layer, consisting of polycaprolactone grafted onto the surface of the silica core.

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School of Life Sciences FHNW

Biocompatible nanoparticles; Indocyanine green (ICG); block copolymer PCL-b-PLLA; grafting from.

Indroduction

IIndocyanine green (ICG), first reported by Fox et al [1], has recently received considerable attention due to its widespread biomedical applications [2]. The fluorescent dye, which absorbs strongly in the near Infrared spectral region leading to strong IR fluorescence emission, received FDA approval for a variety of medical, diagnostic and imaging applications [3]. An increasing number of medical applications such as laser-induced tissue soldering, where tissues are fused together by ICG absorption, require defined locally-confined ICG concentration to guarantee an even and efficient heat transfer. However, application of ICG for *in vivo* imaging and tissue soldering, where contact with body fluids cannot be avoided is limited due to its poor aqueous stability, its photo-degradation [4] and concentration-dependent aggregation. However, these limitations can be overcome by incorporating ICG in a carrier delivery system, which protects the dye in a polymeric hydrophobic environment form exposure to the aqueous environment inside of the body.

Amorphous and mesoporous silica as a carrier exhibits great potential for biological applications, since it is a ubiquitous, non-toxic material and therefore biocompatible. A further advantage is the ease of synthesis with a well-defined structure and a precise size control in the nanometer range [5]. Because of these interesting properties, silica nanoparticles were studied as carrier system to encapsulate ICG.

The aim of the project was to develop a synthetic strategy to improve the stability of ICG and a particular biocompatible nanoparticle system with a size range between 120 and 80 nm carrying a high load of ICG. The first obstacle to overcome was the need to encapsulate ICG in a hydrophobic polymeric environment, to avoid exposure to the aqueous environment inside the body and to stabilize the dye and furthermore to combine it with an inorganic silica nanoparticle core. Based on the foreseen use in a biomedical application (sutureless tissue soldering), the choice of the polymer for the encapsulation of ICG depends on three crucial properties: hydrophobicity, biocompatibility and biodegradability in the body fluid environment. Accordingly, poly(ε-Caprolactone) (PCL), a semi-crystalline polyester, was chosen as the encapsulation matrix. PCL is a well know biocompatible and biodegradable polymer with FDA approval.

A core shell nanoparticle system consisting of a defined silica core of 120–80 nm was developed using the well-known Stöber method followed by a surface amino modification using the corresponding organsilane precursors and finally coated with a hydrophobic PCL layer acting as carrier system for ICG. Since the nanoparticles will be used for biomedical applications, the PCL layer was coated with an additional hydrophilic polymer (Poly-L-Lactide (PLLA)) providing colloidal stability in aqueous solution.

The method for encapsulating the functionalised cores was a 'graft from' anionic coordinated ring opening polymerisation (ROP), catalyzed by tin alkoxides and carried out in a microwave reaction system (110°C under nitrogen atmosphere).

The combination of the inorganic core with the polymeric layer structure considerably improved the stability of ICG in the body fluid and its shelf life (21 days in the dark with almost no loss in dye intensity, resp. observable degradation). First experiments carried out simulating *in vivo* conditions were very successful with regard to both stability and the final tissue soldering application. Figure 1 shows a sketch of the general structure and the SEM micrographs of the final hybrid particles.

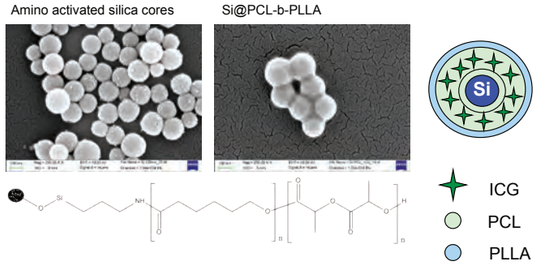

Figure 1 *Anionic coordinated ROP of E-CL from the amino activated silica surface and LLA from the OH-end of PCL: Si@PCL-b-PLLA/ICG*

Results

In order to determine the ICG loading content and entrapment efficiency, the amount of ICG encapsulated into the PCL shell was determined indirectly from the unincorporated ICG residues left in the solvent after encapsulation via UV-Vis spectroscopy at a wavelength of 786 nm. To evaluate the efficiency of ICG entrapment in correlation to the ICG content in the reaction solution, different concentrations of ICG in the reaction volume were tested. It was observed that the highest ICG loading content and entrapment efficiency were obtained with an ICG concentration of 1.6g/l in the reaction solution. The ICG content in NPs was 2.36% and the entrapment efficiency was 87%, indicating that a high amount of ICG from the reaction solution was encapsulated into the PCL matrix.

In order to investigate the colloidal stability of the NPs in aqueous solution, the change of the surface charge after each synthesis step was followed with zeta potential measurements. The zeta potential of the unmodified silica cores with 120 nm and 80 nm diameter was -35.6 and -25.0 mV respectively. Zeta potential of the amino functionalised silica cores decreased to -28.5 and -23.5 mV, due to the positive charge of the amino groups introduced to the silica surface. After encapsulation with PCL, zeta potential decreased to -19.9 and -16.5 mV due to the hydrophobic properties of PCL, while after coating with PLLA zeta potential increased to -27.7 and -23.6 mV. As assumed, the final polymerisation with PLLA made the nanoparticles more hydrophilic, providing the required colloidal stability in aqueous media.

Leaching of ICG encapsulated in the NPs was investigated under physiological conditions (PBS- Buffer). The shelf life of the particles was determined by measuring the fluorescence intensity. Therefore the particles were stored in the dark at RT and 37°C and the fluorescence intensity was determined over a period of 14 days. Fig. 2 shows the stability of ICG loaded NPs suspended in PBS. Very similar emission spectra, recorded after 1, 7 and 14 days with a prominent peak at 786 nm, were obtained for all samples, indicating high stability and very low degradation over the entire period. These results clearly show the successful stabilization of the ICG dye by utilizing organic/inorganic hybrid nanoparticles with no decomposition and no dye leaching out of the matrix. Furthermore photo stability also improved significantly. Intense studies under laser tissue soldering conditions are currently under investigation.

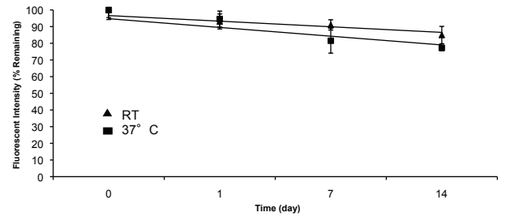

Figure 2 *Influence of temperature on aqueous stability of Si@PCL-l-PLLA/ICG (stored lightpacked) over a period of 14 days. Bars represent the standard deviations (n≥3). Fluorescence intensity indicated as % remaining.14 days at a) RT and b) 37°C.*

Conclusion and Outlook

The approach to synthesizing ICG loaded NPs presented in this abstract demonstrates a new route to stabilizing ICG by embedding the dye in a hydrophobic biocompatible matrix. In order to increase the colloidal stability of the NPs in an aqueous environment as required for *in vivo* applications, the surface of the particles was modified with PLLA. A maximum ICG loading content of 2.36 % of the overall mass was obtained by following this synthetic route. Moreover, the ICG in the NPs exhibits excellent stability against aqueous decomposition. During a period of 14 days no significant change in fluorescence intensity was observed. We therefore conclude that, although the ICG was extremely tightly packed in the NPs, there is no significant self-quenching of the dye. Most probably the singlet oxygen, produced by possible photo decomposition of the ICG dye, is quenched by the polymer, thus inhibiting the further decomposition of ICG.

The silica core has been chosen in first instance to obtain particles in a uniform and controllable size range. In a later stage of the project the synthesis of poly(ε-caprolactone) coated particles with embedded dye and other core matrix materials is foreseen.

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Research Focus Area:
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Funding:
Swiss National Science Foundation (SNSF) within the National Research Programme NRP 64 "Opportunities and Risks of Nanomaterials"

Economic efficiency and benefit to society:
We report on the design and synthesis of highly stable silica core polymer shell NPs acting as a carrier system for the light and highly water sensitive dye ICG. Encapsulation of ICG in the hydrophobic polymer shell circumvents the physiochemical properties of the dye and enables their use for a variety of in vivo imaging applications and novel minimally invasive surgery methods (sutureless laser tissue soldering)

Active load control bedding system for an operating table in hospital environment

Suffering from decubitus ulcers, also known as bedsores, leads to long term treatment of the affected region and contributes significantly to health care expenditure. Acquiring a decubitus ulcer during a hospital stay is often related to time consuming surgical procedures. Therefore a new approach towards an active load controlled bedding system for operating rooms is being investigated.

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School of Life Sciences FHNW

Keywords: Decubitus ulcer, prophylaxes, prevention, active bedding, operating table

Indroduction

Decubitus ulcer, known as a bedsore or pressure ulcer, is often induced by an increased external local load or pressure on tissue. This results in squeezing the tissue towards underlying bones and decreasing or disabling peripheral circulation and perfusion. Typically tissue not protected by muscles or fatty tissue is affected. Therefore anatomically exposed bony regions of the human body such as the sacrum, ischium and calcaneus are subject to an increased risk of developing a decubitus ulcer. In addition to the applied mechanical load the duration of exposure of the load increases the risk of developing a decubitus ulcer [1]. Therefore bedridden persons with limited movement opportunities are particularly affected. This risky situation is reflected in different scenarios, where prolonged periods of lying down without repositioning the body occur, for instance in home care or intensive care.

Besides the impact on the life of individuals, a decubitus ulcer is also a significant clinical and financial issue for health care providers. A decubitus ulcer may cause a longer hospital stay. The German Robert Koch Institute estimates a financial burden of around 2 billion Euros in 2002 in Germany for the health care system [2], while other experts estimate annual costs for UK from 1.4 to 2.1 billion GBP corresponding to 4% of the total National Health Service (NHS) expenditure [3].

Besides the home care or intensive care scenario as a risky situation, the operating room (OR) is getting more and more attention. This environment may increase the risk of a pressure ulcer, as patients are kept immobile for long periods of time. Due to anaesthesia procedures, patients are unable to shift their weight, feel pain or complain. Enhanced anaesthetic procedures enable surgeons to perform complex and time-consuming interventions, prolonging the operation time and increasing the risk of a decubitus ulcer. Approximately 23% of the total number of decubitus ulcers developed in hospital are acquired intraoperatively [4]. In addition certain anaesthetic agents may decrease peripheral circulation and perfusion, resulting in an increased risk of developing a decubitus ulcer [5].

Nowadays strategies to decrease this risk in an operating room environment are limited to reducing the load by optimizing mat materials and pressure distribution surfaces. So far no active or controlled load regulating system is known. Within this project we investigated a novel approach for an active support system, capable of reducing local pressure on tissue by an active load controlled bedding system.

Results

The approach to a smart decubitus prophylaxis system integrated into an operating table focuses on detecting the load distribution applied from patient to the OR-table and relaxing overloaded regions by lowering the height within this region. Therefore an array-like structure of single elements containing load detection and a mechanism for changing height were developed and a demonstrator built.

Each single element contains a sensor (force sensing resistor), detecting the force applied to that area. It is located at the top of the element and is covered by a force distribution plate to ensure homogenous load distribution on the sensing element. The mechanics of each element is based on two rollers, driven by a worm gear, approaching or moving away from each other. The rollers create a height change of a surface with a tilted sub-construction, as shown in Figure 1 (top). The gearing is designed to be self-blocking; only during the height adjustment is an external power source required. For the demonstrator the mechanics of each element, including the gearing, was generated by rapid prototyping. Multiple elements are arranged in an array structure (Fig. 1), a modular rack suitable to replace single modules of the commercial OR-table (Fig. 2).

The results of a closed loop active load control of a single element which ignore the history of the element are shown in figure 3, where repetitive application (indicated by blue arrows) and removal (indicated by green arrows) of a load are shown. As soon as the load exceeds the threshold value the height changing element is lowered until the applied force drops below a second threshold value. By removing the load completely, the element will rise to its initial position.

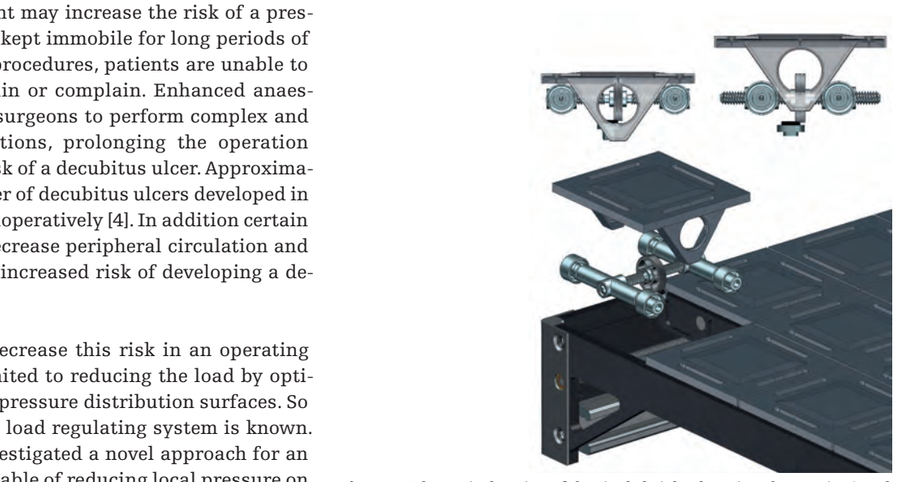

Figure 1 *Schematic drawing of the single height changing element (top) and the integration within a mechanical support structure (bottom)*

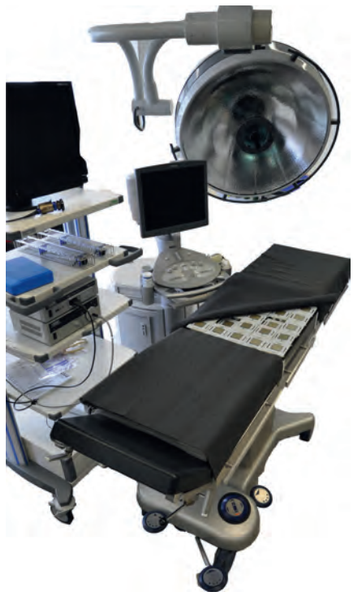

Figure 2 *Integration of a 5x5 demonstration module within an OR-table (OR demo lab)*

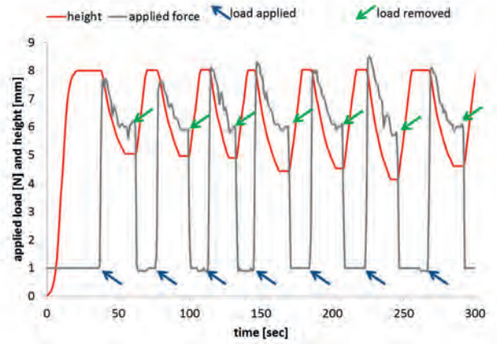

Figure 3 *Repetitive application (blue arrows) and removal (green arrows) of load (grey) resulting in a change of height (red) of the single element.*

As the modified OR-table needs to provide a partial area of transparency for x-ray imaging, there are major restrictions concerning the material used within this x-ray window. Materials with low x-ray attenuation whilst offering high mechanical stability, such as carbon fibre, are of particular interest as a construction material. Furthermore the active devices for changing height, in particular the electric motors, are placed outside this window and positioned below the element using a linear stage during actuation only. If no action is required, the stage moves outside the x-ray window into a parking position. This concept reduces the number of electric motors required significantly while enhancing x-ray transmission capabilities. In the current demonstrator the 2 cm full height lowering of all 25 elements can be realized within ten minutes.

Various approaches to control the height are currently under investigation. Based on up-to-date and preceding data from the elements, including neighbouring elements, the OR-personnel will receive a recommendation to shift the height of single or multiple elements on a display if a recommended threshold value is exceeded. The decision to change patient positioning has to be verified and approved by OR-personnel. If the change is accepted, an electric motor will lower the affected element and/or raise the neighbouring ones by up to two centimetres until the applied load decreases to a predefined acceptance level.

Conclusion and Outlook

A demonstrator proving the feasibility of the linear stage concept was created and integrated into a commercial OR-table in our demo lab. Within this feasibility study, we set up an active bedding module as a demonstrator for a decubitus prophylaxis during surgical procedures. As the current demonstrator is not manufactured in a final way, the mechanical properties do not meet the requirements yet. Nonetheless the basic concept was successfully verified. The element footprint, will be addressed in more detail, requiring a complete active bedding system. Only single elements have been evaluated. New strategies of control are being developed this demonstrator offers a promising experimental set-up for elaborating and testing these strategies.
Creating this demonstrator successfully verified the proof of concept and allows us to proceed with the development of an active load controlled bedding system.

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Research Focus Area:
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Funding:
Co-financed by Commission for Technology and Innovation (CTI)
Economic efficiency and benefit to society:
Avoiding a decubitus ulcer will enhance the quality of life of the treated persons, while reducing the duration of the hospital stay and reducing the expenditure of the health care system significantly.

Medical imaging: A robust and accurate segmentation of the knee bones from computer tomography data

Medical Imaging plays a central role in the cost-effective use of patient-specific tools in surgical technique: The production of cutting blocks – for knee-joint implant positioning – requires a precise segmentation of femur and tibia from preoperatively acquired image data. Due to low bone density and osteophytes, this segmentation is done manually by experts and requires several hours. Here a novel, robust and accurate segmentation method for a medical planning system is described.

Alex Ringenbach
School of Life Sciences FHNW

Keywords: CT-Data, Knee Bones, Segmentation, Statistical Shape Model, Fast Marching

Indroduction

For the accurate implant positioning of a knee-joint replacement, it is increasingly common to use custom-made cutting blocks (Fig. 1 left), which indicate the cutting plane to the surgeon. The advantage of this method over conventional surgery is the simpler alignment of the implants, a shorter operation time as well as fewer instruments [1].
The specific geometric information for the cutting blocks has to be taken from preoperatively acquired image data, this is a key aspect of medical imaging and is called segmentation. Due to low bone density and osteophytes (Fig. 1, right) the automated segmentation of knee bones from computer tomography (CT) data can be a major challenge. Osteophytes are an overgrowth of bone tissue, especially in older people; they are filigree and can hardly be captured by prior knowledge based segmentation approaches.
As part of an industrial project, we have developed a hybrid segmentation method - essentially based on statistical shape models and the Fast Marching algorithm, which is stable and has good accuracy

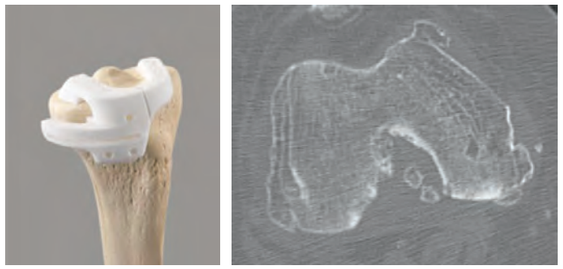

Figure 1 *Left: cutting blocks for knee-joint implant. Right: CT slice image from femur with low bone density and osteophytes.*

Method

Our approach to the knee joint segmentation consists essentially of two steps: first, a robust pre-segmentation is performed (a knowledge based approach with a statistical shape model) to identify and separate the bones. This is followed by a sensitive fine-segmentation (a locally data-driven approach with non-local control parameters) in a narrow band around the pre-segmented boundary to detect the local nuances and osteophytes on the bones as accurately as possible.

With the statistical shape model (Fig. 2) we capture the prior knowledge of the shape variability of knee bones. For that we used 30 CT data sets and computed (for femur, tibia und patella) the average models and their shape variations [2] [3].

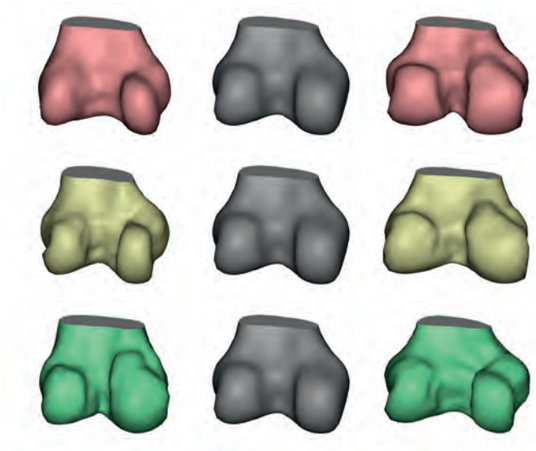

Figure 2 *Statistical shape model of femur (limited to knee-area). The three rows show the first three shape variations (± 2σ with respect to the average shape in the middle).*

In a first step the statistical shape model was registered with the image data (Fig. 3, left): by matching the average models with the image to get an initial position and then by adapting the first five shape variations iteratively [2].
Due to the limited statistical data and the presence of osteophytes, which are not captured by the statistical model, the automated pre-segmentation leads to a mean deviation error of 2.2 mm – compared to manual segmented data.

In a second step, the bones were approached from the outside in a narrow band with the front-propagation Fast Marching method [4] (Fig. 3, right). This algorithm describes a monotonically increasing propagation front, defined by the initial position and by the speed function $F(x) \geq 0$. One possible definition of the speed function to stop the front propagation in the region of edges is $F(x) = 1/(1+|\nabla f(x)|^{\alpha})$, where $f(x)$ represents the image data.

This view of Fast Marching – as an initial value problem – shows the similarity to the region-growing algorithm and emphasizes the locally sensitive acting mechanism, which is needed for the detection of filigree structures. On the other hand, the Fast-Marching method (in the boundary value problem representation) solves the Eikonal equation of optics, which determines the minimal optical distance [5]. This explains that the Fast Marching method determines – by using an edge controlled speed function – an edge-weighted distance to all propagation points. And this is the advantage of the Fast Marching method – compared e.g. to the region

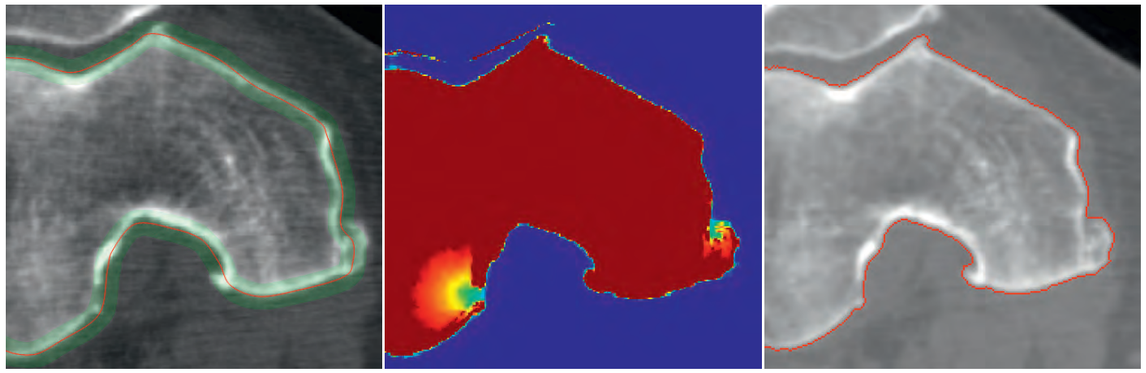

Figure 3 *Left: the red-line shows the pre-segmentation based on the statistical shape model. Middle: the propagation field of the Fast Marching method in a narrow range around the pre-segmentation. Right: the fine-segmentation. The cyan-yellow-colored part in the propagation field (middle) indicates locally weak bone edges in the image data (left) which are well segmented due to the cumulative edge information (right).*

growing approach –, it provides an additional non-local parameter to control the local acting segmentation process, within the narrow band. So, also weak edges can be well captured. With this fine-segmentation step the mean deviation error is reduced to 0.3 mm – compared to manual segmented data.

Results

A hybrid segmentation method was developed for knee bones form CT data which is stable and has good accuracy. The model-based approach guarantees robust detection and separation of femur, tibia and patella for all CT images, and the local acting front propagation method Fast Marching improves accuracy for most CT images to a mean deviation error of 0.3 mm. The implementation of the algorithm in a planning tool for designing cutting blocks has reduced the processing time for the whole workflow from 90 or more minutes to less than 10 minutes. It has already been successfully used more then three thousand times.

Conclusion and Outlook

Advanced image segmentation methods are manly based on global optimization, and therefore robust but not always accurate enough. With the Fast Marching algorithm a locally post segmentation is realizable without losing the benefits of the global approaches. In a next step the the planning system will be expanded for MRI images.

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Förderfonds Aargau, canton Aargau

Economic efficiency and benefit to society

The implementation of our algorithm in a planning tool for cutting blocks has reduced the manually processing time (over the whole workflow, for trained staff) from 90 or more minutes to less than 10 minutes.

Acceleration Measurement for objective symptom evaluation during Deep Brain Stimulation surgery

Deep Brain Stimulation (DBS) is a common neurosurgical procedure for relieving movement-related disorders such as Parkinson's disease. However due to an incomplete understanding of its mechanism of action and suboptimal exploitation of intraoperative data, target selection is not yet optimal. Our aim is to evaluate the feasibility of objectively assessing the clinical effect during intraoperative stimulation tests using acceleration measurements.

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Keywords: Deep Brain Stimulation, Parkinson's Disease, movement related disorders, acceleration measurements

Introduction

Deep brain stimulation (DBS), the electrical stimulation of structures deep within the brain through surgically implanted electrodes, is now an effective and widely-used method of treating neurological movement related disorders (tremor and rigidity) such as Parkinson's Disease (PD)[1]. During a typical surgical procedure, a thin probe is stereotactically inserted along a preoperatively calculated trajectory, which has been determined on the basis of magnetic resonance imaging (MRI) and computed tomography (CT).
As the action mechanism of DBS is not fully understood, optimal target definition is difficult and thus most groups use complementary intraoperative methods. In addition to the preoperatively obtained anatomical data, further information about the structures along the electrode trajectory is acquired. For example, by using microelectrode recording (MER), neuronal activity deep in the brain can be recorded [2] which is analysed regarding the discharge pattern. When MER is performed, recordings are made along up to five trajectories in the volume of interest. This is to identify the boundaries of the different structures, in general starting up 10mm in front of the target and going down in 0.5 to 2mm steps until the target is reached or even 1 to 5 mm beyond it. Most centres also perform intraoperative stimulation along the trajectories to evaluate the clinical effects on rigidity and tremor at increasing stimulation voltages, determining the thresholds for clinical effects (subjective threshold) and side effects at each anatomical measurement point. The final surgical target in which the chronic stimulation electrode is implanted afterwards is chosen by the neurosurgeon by mentally integrating the multitude of patient information collected before and during the surgery.
DBS has many advantages over other surgical treatments of movement disorders, but there are a few uncertainties associated with it as well [3]. The targeting procedure is the part of the surgical protocol that can still be improved from an engineering point of view [4]. Existing data can be acquired more objectively than is done today, for example with the aid of quantitative movement analysis via sensors. As the data interpretation for target selection is based on all of the obtained measurements, it would be desirable to optimise data presentation and visualisation. These are the main aims of the current research project.The basic idea is to assess the patients' symptoms objectively and help the doctors visualize them along the planned trajectory on the MRI/CT images. Clinical studies in Basel and Clermont-Ferrand (France), including 30 patients, have been approved by the local ethics committees. The objective assessment is achieved by measuring the acceleration of the wrist of the patient (for tremor analysis) and neurologist (for rigidity analysis) before, during and after the DBS surgery. An accelerometer, (device measuring acceleration) placed inside an in-house developed plastic case, is tied to the patient's/neurologist's wrist (Fig. 1) and connected to a laptop which uses an in-house developed application to record data and display it in graphical form. Data from the accelerometer is recorded without any stimulation (i.e. baseline), during the MER recording and the test stimulation.

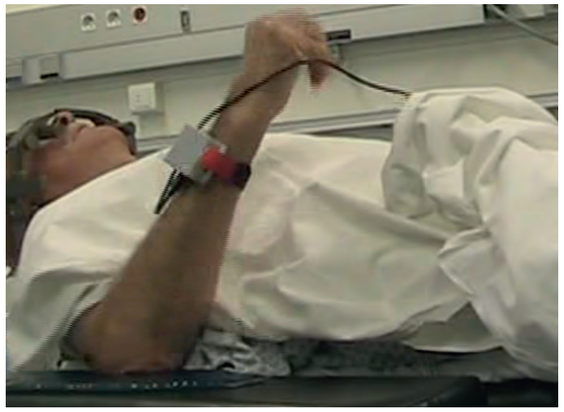

Figure 1 *Accelerometer tied to the patient's wrist for evaluation of tremor.*

Results

A protocol was established where accelerometer data is continuously recorded at every stimulation position for each trajectory for numerous stimulation amplitudes (Fig. 2A).The data recorded during the surgery is post-operatively grouped according to the stimulation amplitude and statistical features (standard deviation, energy, entropy) are extracted from it (Fig. 2B). The values of these features before the subjective threshold were statistically compared to the ones at the subjective threshold. So far, in most cases results confirmed the presence of significant clinical changes. For tremor, a statistically significant change ($p<0.01$) was found for signal entropy, energy and standard deviation. For rigidity, a statistically significant change ($p<0.01$) was found for signal energy and entropy.

In a second step, the calculated features are then normalized to the baseline values and used to identify an accelerometer threshold (amplitude at which accelerometer data alone suggests a change in symptoms). Such thresholds were determined for every measurement position on all the trajectories.

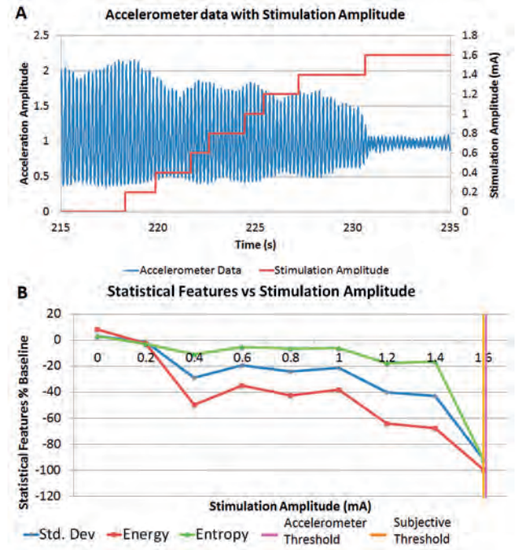

Figure 2 *A: Raw accelerometer data and stimulation amplitude against time. B: Extracted mathematical features against the stimulation amplitude.*

The calculated thresholds were graphically compared with the subjective threshold (Fig. 3).
Then the final electrode implant location is postoperatively selected which would have been chosen for the chronic electrode based on the accelerometer thresholds and the clinically defined side effect thresholds. It is compared to the real final electrode implant location intraoperatively chosen based on the subjective clinical evaluations (Fig. 3). The signal energy was observed to be the most sensitive feature showing highest change compared to the baseline. In most cases, the accelerometer threshold was lower than the subjective threshold. Approximately one third of the implant locations would have been different based on accelerometer data than on the subjective evaluation due to a higher difference between clinical and side effect thresholds.

Conclusion and Outlook

The initial results from this project have demonstrated the feasibility of performing objective assessments using mathematical features (signal energy, entropy and standard deviation) extracted from the acceleration signal of the patient's or the neurologist's wrist. New statistical features based on frequency analysis are being considered and continuous changes are being made to the software and hardware to improve data acquisition and visualization. The possibility to visualize the planned trajectory with the effects and side effects on the images is already implemented. Real-time analysis of the accelerometer data and its visualization along with other intra-operative data, have been planned for future updates of the software. The introduction of these technologies in the OR will probably result in greater objectivity of the surgeon's decision on the final target and trajectory compared to the current method. The measurements will allow further individualisation of functional parameters and might increase electrode positioning quality as well as the safety of the target identification procedure. This has to be confirmed after the inclusion of all 30 patients. In addition to the practical aspects these measurements and their correlation with clinical evaluations and MER data might generate new information and knowledge useful for the development of the human connectome and its correlation to the functional connectivity of the human brain.

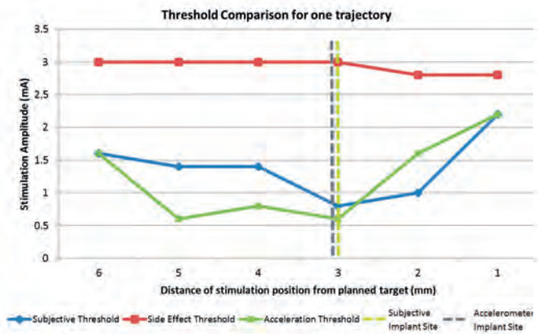

Figure 3 *Comparison of different thresholds and of the final implant site based on accelerometer data and subjective clinical evaluations.*

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Funding:
Swiss National Science Foundation (SNSF), Germaine de Stael foundation

Economic efficiency and benefit to society:
Objective assessment of symptoms during Deep Brain Stimulation surgery and better visualization of intra-operative data will allow doctors to more accurately define patient-specific targets for treatment of movement related disorders, hopefully resulting in better clinical results. Furthermore new knowledge about the mechanism of action of the stimulation may be created.

Supporting Strategic Planning with Interactive Visualization: A Case Study of Patient Flow Through a Large Hospital

Hospitals routinely collect large amounts of data that can be used to improve administrative processes, in addition to their primary clinical purpose. Strategic infrastructure planning, for instance, can be supported by the analysis of enriched data relating to patient flow through a hospital. Using our dedicated visual analysis software, analysts were able to identify several sub-systems of clinics that will play a central role on the future hospital campus.

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School of Life Sciences FHNW

Keywords: clinical informatics, interactive visualization, visual data analysis, patient flow, hospital planning

Introduction

Hospital sites develop in an evolutionary manner over a long period. This usually leads to physical and organizational layouts of the facilities that are no longer optimal after a certain time. Strategic planning with time horizons of 25 years and more provides the opportunity to correct this degeneration and optimize the layout when the campus is enlarged, new facilities are built, or old ones replaced.

The optimal configuration of departments, their organizational units and technical facilities is not always evident. Questions such as "where should the emergency department be placed, and if we locate it in a new building, do we need an additional radiology facility?" should be answered based on evidence and insights rather than intuition, subjective opinions, or obsolete experience [1]. The idea therefore was to use past real data to identify existing clusters of organizational units that are related based on what they actually do, and not on where they are placed in the organization chart. With these insights, it should be possible to define future sub-systems of organizational units and medical functions which are optimized for efficiency. These new sub-systems can then be characterized again with the past data for further analysis and communication to stakeholders.

We present a case study where we collected, combined and enriched data from a large university hospital, and used interactive visualization to access, analyze, and interpret the data to support strategic infrastructure planning.

Results

In our project, information from several sources of the hospital's IT-infrastructure was used and linked. We collected one full year of data from 40 clinics comprising 300 organizational units that treated 40,000 cases from 30,000 in-patients, with 320,000 transfers between the organizational units.

With all the data integrated and available, the next challenge was to render it usable for the planning experts. For the type of problems found in our case study, analysts often only have vague notions of what they are looking for ("I know it when I see it"). It is therefore crucial to make the data visible from various angles, and to provide highly interactive tools to identify interesting patterns and access details in context. We developed a visual analysis application to support analysts in making sense of the collected data. The application offers four principal views (Fig. 1):

– Organizational (Fig. 1, top left): Shows the organizational structure and how the actual medical activities shape the administrative space. A circular layout is used to arrange all the major clinics of the hospital. Circular layouts have proven effective to show genetic sequences and relationships between genomic positions [2]. We adapted this technique to show the flow of patients in relation to the organizational structure of the hospital.

– Systemic (Fig. 1, center): Reveals the operational structure as it emerges from patients flowing through the hospital. The movement of patients between clinics effectively creates a network of relationships, where clinics that move more patients between them are closer, or more similar, than clinics with fewer or no transfers. To make this network visible, we employ a multidimensional scaling algorithm [3].

– Topographical (Fig. 1, top right): Shows the actual physical situation as a structure that evolved through many individual decisions. The topographical view shows the patient transfers on a geographical representation of the current hospital campus.

– Chronological (Fig. 1, bottom): Adds the dynamic view on how events and quantities change over time. The in- and out-transfers for each day are shown as a mirrored stacked bar chart. The mirroring makes it easy to spot imbalances between in- and out-flows. The net flow for each day is cumulated and over-plotted as a black line. This essentially shows the number of patients that are present in a clinic on a particular day.

In order to rationalize and interpret the insights and hypotheses generated by the four principal views, it is necessary to drill-down to the level of individual cases. Cases can be filtered either by the organizational units that they have visited on their journey through the hospital, or by various categorical or numerical case attributes (e.g., destination after discharge, diagnosis, length of stay). In a separate view, we show all the filtered cases at the same time. In order to display several hundred case histories in parallel, their representation is condensed to a single line that is only one pixel high, but still preserves the essential information about the case history (Fig. 2).

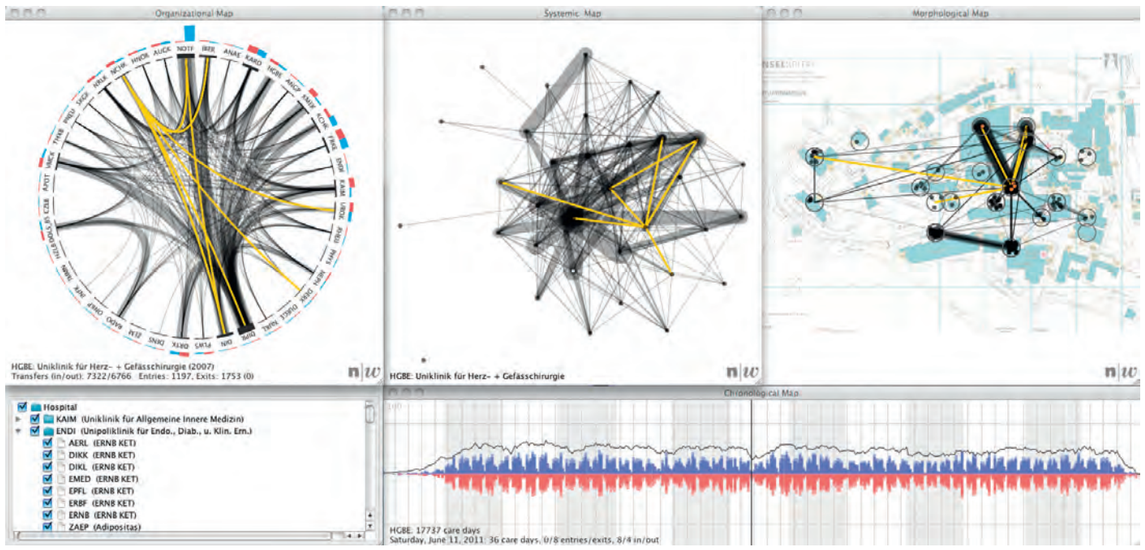

Figure 1 *The flow of patients through a hospital. Yellow lines show the trajectory of a case treated for abdominal metastasis during a 4-week stay.*

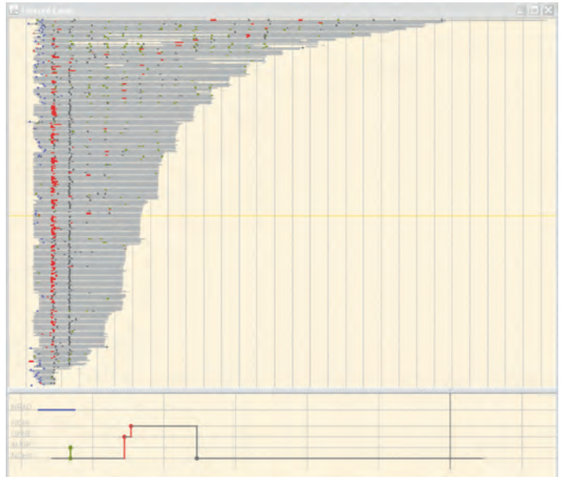

Figure 2 *Cases are displayed in parallel to find patterns, e.g. the variation in procedures and duration of all cases for the diagnosis "craniotomy".*

Conclusion and Outlook

Our analysis with this application allowed us to gain an overview of the big picture of the hospital system. By making the flow of patients visible, we were able to contrast the hierarchical organizational structure with the actual implemented working relationships. This showed the difference between the operational structures that developed through medical consequences, and the theoretically defined organizational structure. Based on this difference, we were able to describe new sub-systems and identify an organizational form that corresponds to the current actual needs.

It was not really a surprise that the core functions of a hospital such as emergency department, operating rooms, and diagnostic functions appeared in the center of the system, but it was not expected to be so pronounced. A new insight was the role of the cardiology clinic as an important service center for diagnostics. This led to the decision to also assign it a central role on the campus. Also new was the interpretation of the role of the clinic for internal medicine as being primarily a receiving station for the emergency room, with the further distribution into the specialized clinics taking place only one or two days later.

In summary, our case study has shown that there is a wealth of interesting information in the data that is collected in large hospitals, beyond their immediate and intended use. We took a different view of electronic health records to support strategic infrastructure planning.

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Funding
Bern University Hospital
Economic efficiency and benefit to society
This project saves a great deal of money and improves well-being.

The Interplay of NiTi shape memory alloys and human Bone Marrow-Derived Mesenchymal Stromal Cells

NiTi shape memory alloys (SMA) have unique mechanical and physicochemical properties that are attractive for a wide variety of biomedical applications. With the ultimate goal of fabricating complex 3D NiTi implants for orthopaedic and dental applications, we assessed the biocompatibility, proliferation and osteogenic differentiation of human bone marrow-derived mesenchymal stromal cells (hBMSC) cultured on additive manufactured (AM) NiTi disks.

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Keywords: differentiation, stem cells, additive manufacturing, implant development, NiTi shape memory alloy (SMA)

Introduction

Selective laser melting (SLM) is an additive manufacturing (AM) process, which enables the fabrication of CAD-designed complex-shaped and highly porous 3D structures [1]. Using this AM-technique, NiTi-SMA-based constructs are produced [2-3]. NiTi-SMA exhibit unique mechanical and physicochemical properties that could benefit a wide variety of biomedical applications [4]. Ultimately, we aim to fabricate and validate complex-shaped 3D NiTi constructs as implants for orthopaedic and dental applications. Therefore SLM-fabricated NiTi disks (Ø 14 mm) were used as substrates for human Bone Marrow-Derived Mesenchymal Stromal Cells cultures. Cell cultures were performed in order to assess biocompatibility of substrates used as well as the proliferation and differentiation capacity of hBMSC on those substrates. Besides *NiTi*, passivated NiTi (*pNiTi*), SLM-Ti (*Ti*), sand-blasted and acid etched SLM-Ti (*Ti SLA*) and commercially produced and clinically used SLA Ti (*Ti ref*) [5] were used as substrates and compared to *TCP* (tissue culture plastic [6]).

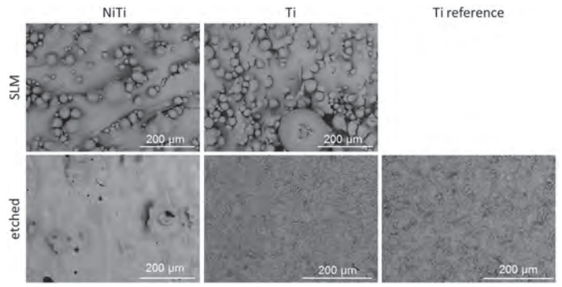

Figure 1 *SEM images of metallic substrates. Upper panel depicts surface morphology of untreated samples. Lower panel depicts surfaces post associated treatments.*

Results

The substrate morphology was assessed by scanning electron microscope (SEM) imaging and is depicted in figure 1, revealing the surface topography of all substrates tested. The native surfaces of *NiTi* and *Ti*, both produced by SLM, are solidified casts with incorporated spherical particles, being sintered powder residues. These attached particles give the native surface a charactzeristic morphology [7]. *Ti SLA* and the clinically proven *Ti ref* are equivalent surfaces with a very rough surface both on the micro and nano scale. The difference between both titanium materials is the production process of the starting material, the former was produced generatively, whereas the latter was made conventionally. The *pNiTi* surface is free of spherical particles due to the etching process and exhibits micro scale structures (moon-like landscape). All substrates tested were found to be biocompatible according to ISO 10993-5 [8]. 80% of seeded hBMSC attached to the surfaces tested within 12 hours and thereafter proliferated exponentially, with similar growth rates as on *TCP*. hBMSC cultured on metallic substrates exhibit growth rates of 0.133 ± 0.026 1/d comparable to the growth rate obtained on TCP (0.128 ± 0.020 1/d), with the maximal growth rate obtained on *NiTi*, whereas the minimal growth rate was obtained on *Ti SLA*.

As illustrated in figure 2, cell morphologies of hBMSC cultured in culture medium (CM) or osteogenesis inducing medium (OM) for 21 days are similar within the groups, elucidating a dense extracellular matrix (ECM) layer beneath the cell

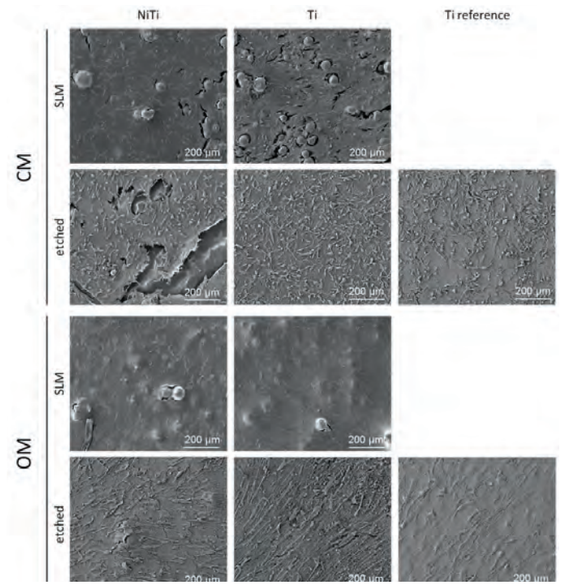

Figure 2 *SEM images of hBMSC cultured on metallic substrates in culture medium (CM) and osteogenesis inducing medium (OM).*

layer with randomly orientated cells in CM versus a directed cell orientation in OM. In both media conditions cells cultured on SLM-based, untreated substrates (NiTi, Ti) are more sprout as compared to spindle-shaped cells on post treated substrates. hBMSC produced a dense layer of ECM on the metallic substrates and covered the ECM in multiple layers, as revealed by confocal fluorescence (data not shown).

In order to assess osteogenic differentiation capacity of hBMSC cultured on metallic substrates, cells were cultured either for 14 or 21 days in OM and both gene expression for BSP by quantitative real-time PCR and matrix mineralization by alizarin red staining were examined. Bone sialoprotein (BSP) is a component of mineralized tissues such as bone and calcified cartilage. It is a significant component of the bone extracellular matrix. Gene expression measurements of BSP revealed an up-regulation for cultures in OM as compared to CM on all substrates (Fig. 3). Nevertheless, in CM conditions hBMSC cultures on *NiTi* express the smallest amount of BSP, almost at the level of post expanded cells (dotted line). Additionally, alizarin red staining revealed high ECM mineralization during 21 days of culture in OM although the donor used does not exhibit a high intrinsic matrix mineralization capability (TCP versus metallic substrates). In CM the matrix mineralization occurs as well but to a lesser extent.

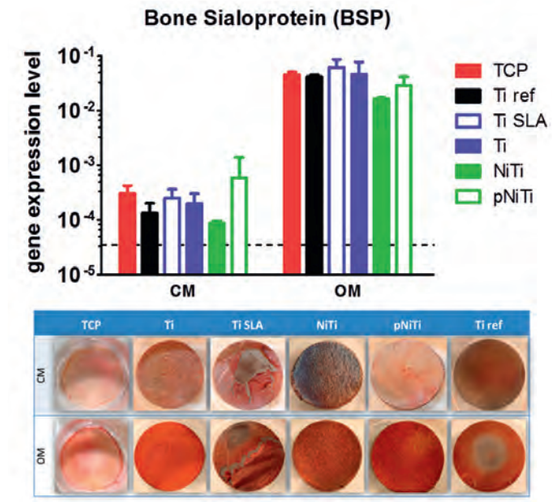

Figure 3 *A gene expression level normalized to GAPDH (dotted line = post expansion expression level) post 14 days of culture, B Alizarin Red staining of hBMSC cultured for 21 days.*

Conclusion and Outlook

The growth rates of hBMSC on metallic substrates are equivalent to growth rates on TCP indicating high cytocompatibility and good hBMSC proliferation capacities. SEM and confocal fluorescence imaging identify hBMSC on top of a dense ECM layer on all substrates tested.
Considering the up-regulation of BSP expression and the highly positive alizarin red staining in OM, the permissibility of all substrates tested to osteogenic differentiation is given. At the same time *NiTi* seems to facilitate maintenance of the progenitor fate in CM, suggesting a binary effect depending on the biochemical signals available. Summarizing these results, SLM-NiTi is a promising material for the design of customized load-bearing implants.
Currently, further studies are being carried out to analyze hBMSC performance in terms of proliferation and differentiation capacity on specifically designed and generatively produced 3D constructs in order to further confirm the promising 2D results for the utilization of SLM-NiTi based materials as implants in the dental and orthopaedic fields.

The utilization of bare NiTi as an implant material can be suggested, due to the fact that small numbers of progenitor cells from bleeding marrow, for instance, can colonize the implant surface and further differentiate down the osteogenic linage, when supplemented with proper nutrients and growth factors.

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Funding:
Swiss National Science Foundation (SNSF) and Commission for Technology and Innovation (CTI) within the National Research Programme NFP 62 "Smart Materials".
Economic efficiency and benefit to society:
The interdisciplinary collaboration between the University of Applied Sciences Northwestern Switzerland, the University of Basel and the University Hospital of Basel is developing additive manufactured shape memory materials for a new generation of biomedical engineered bone implants. These smart implants with shape memory properties and specific surface topography open new perspectives of biofunctionality.

Size Reduction of Liposomes with a novel Type of Stirred Bead Mill (Nanomill)

The potential of liposomes as carriers for drug delivery and drug targeting has frequently been reported but the production of liposomal formulations on an industrial scale remains a challenge. Consequently a novel nano-milling unit has been developed and investigated. The new nanomill fulfils the GMP standards of the pharmaceutical industry and remains entirely closed also when cleaned, sterilised and prepared for another batch.

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Keywords: Pharmaceutical process engineering, pharmaceutical technology, liposomes, nanomill, stirred bead mill, CIP-SIP

Introduction

Over the last years the application of liposomes in the pharmaceutical, cosmetics and food industries has elicited novel breakthroughs and products [1]; e.g. the encapsulation of cheese ripening enzymes in liposomes [2], skin care preparations for the treatment of dry skin [3] and different drug delivery systems [1]. Clinical applications in the field of drug delivery and passive targeting of solid tumors have demonstrated their potential for pharmaceutical applications. However, the production of liposomal formulations on an industrial scale remains a challenge. Ideally, an industrial production scheme should be versatile, simple, robust and cost-effective. Up to now, the large scale production of liposomes with a definite size requires high pressures and high shear rates; this entails the disadvantage of generating mechanical and thermal stress at the same time.

This research project had two major targets: The development of a novel type of nanomill dedicated to the production of liposomes and the determination of the influence of the main operating parameters necessary to form liposomes. Therefore multi-lamellar large vesicles were stressed in the novel "Concept Mill", patent pending, (Willy A. Bachofen AG, Muttenz, Switzerland) which has been developed not only to meet the requirements of liposome production but also the requirements of the pharmaceutical industry with regard to the nanomilling of poorly water soluble drug substances.

Figure 1 *New reverse flow milling chamber*

Figure 2 *Prototype of nano-milling unit*

Results

Stirred bead mills consist of a closed cooled cylindrical vessel fitted with a stirrer and filled with grinding beads – the milling chamber. The remaining volume in the milling chamber is filled with a suspension of the product to be ground, in this case with the pro-liposome solution containing multilamellar large vesicles. Stirrers with different geometries can be used for the agitation of the beads and the suspension. But the core of the "Concept Mill" is an entirely new process chamber, which is integrated into a milling unit ready for production on the kilo-scale.

Furthermore the milling unit fulfils the high good manufacturing practice (GMP) standards of the pharmaceutical industry and remains entirely closed, even also when the unit is being prepared for another batch. This is a world first.

The design of this innovative process chamber underwent a radical change: vertically arranged, ready for gravimetrical filling with grinding beads, suspension flow from bottom to top and conversely, top down unloading of grinding beads. The chamber has been optimized with regard to the flow conditions both in milling mode and in emptying mode. Complete emptying is ensured by the patented WAB DYNO accelerators which generate a reverse flow inside the process chamber strong enough to carry all grinding beads out of the closed system. Furthermore, the unit is ready for cleaning and sterilization in place (CIP / SIP).

The unit is designed to reduce the size of liposomes down to approximately 100 nm as well as to load them, e.g. with poorly water soluble drug substances. For this purpose experiments were conducted in circular mode with yttrium stabilized zirconium grinding beads. The beads ranged from 180 to 250 µm in diameter; this interval was found to be optimal for our purpose as it was possible to achieve a higher percentage of product liposomes smaller than 105.7 nm at a sustainable specific energy input. Approximately 65% of the 500 ml cylindrical mill chamber was packed with grinding beads and filled with the pro-liposome solution. The temperature can be controlled by an external oil thermostat.

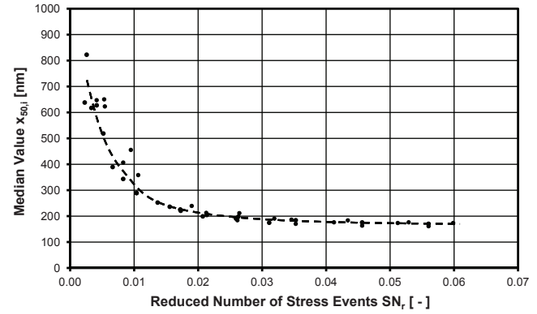

Figure 3 *Comparison of liposome size reduction result vs. reduced stress number SN_r*

The pro-liposome solution with a concentration of 10 mmol/l was produced by thin lipid film hydration. First ~60 % phosphatidylcholine (PC) from egg yolk and 95 % cholesterol were dissolved in a mixture of chloroform and methanol in a 2:1 ratio. The solvent was removed by evaporation under vacuum at 50°C. A thin lipid film remained on the side of the round-bottomed flask, which was then hydrated with an adequate amount of phosphate buffered saline (PBS, pH 7.4) at 50°C. The particle size of the liposomes was analyzed by dynamic light scattering using a Zetasizer Nano ZS.

The new stirred bead mill allows gentle stressing of the liposomes under controlled conditions. The size of liposomes produced correlates directly to the specific energy brought into the liposome suspension, which is the energy input into the milling chamber divided by the stressed product mass. Consequently, the size of the liposomes can be controlled by the specific energy input. This energy input is affected by the stirrer tip speed, the geometry of the stirrer, the grinding beads and the filling ratio of grinding beads [4].

The specific energy $E_{m,P}$, understood as an integral parameter, describes the influence of different operating parameters. It can be also defined as the product of stress energy provided by the grinding beads (SE_{GB}) and the number of stress events (SN_P) [4].

$$E_{m,P} \propto SE_{GB} \cdot SN_P$$

In order to obtain the optimal set of operating parameters in case of nano-milling of inorganic materials the optimum stress energy has to be determined first: The question *"Is the energy for particle breakage high enough?"* has to be answered as the stress energy is dominant for each milling event. However, for organic materials, especially for structures like cells, another concept leads to promising results [5]: the required stress energy for cell disintegration is very low because the strength of such organic particles is weak and therefore the number of stress events is dominant. Since liposomes are more similar to cells than to inorganic crystals, a reduced number of stress events (SN_r) has been proposed to describe the result of the size reduction of liposomes:

$$SN_r \propto \varphi_{MK} * (1 - \varepsilon) * n * t * \frac{x}{d_{GB}}$$

with:

SN_r	[-]	:=	reduced stress number
ϕ_{MK}	[-]	:=	filling ratio of beads
ε	[-]	:=	porosity of bead fill
n	[s^{-1}]	:=	stirrer speed
t	[s]	:=	time of size reduction
x	[m]	:=	product size/diameter of liposomes
d_{GB}	[m]	:=	diameter of grinding beads

The result of size reduction in a stirred bead mill can be fully described by the concept of the stress number (the more stressing events, the better the result), independent from the stress energy exchanged at each milling event inside the mill, fig. 3.

Conclusion and Outlook

During this study the influence of the main operating parameters necessary for the size reduction of liposomes with nanomills was determined. It has been revealed that the result of size reduction with this type of mill can be described by the concept of the stress number which, consequently, can be used to control the size reduction of soft organic particles. Furthermore this mill has been developed not only to meet the requirements of liposome production but also the requirements of the pharmaceutical industry with regard to the nano-milling of poorly water soluble drug substances. The novel nanomill was developed, built and presented at the ACHEMA 2012.

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Partner:
Willy A. Bachofen AG Maschinenfabrik

Funding:
Co-financed by Commission for Technology and Innovation (CTI)

Economic efficiency and benefit to society:

The novel nanomill fulfills the high GMP standards of the pharmaceutical industry and is ready for SIP/CIP as this unit remains closed for filling, bead and product emptying, or cleaning. This new milling unit allows fast batch changes and short cycle times so that production can be more efficient and cost-effective.

Ultrasound-Based Process Analytical Tools for Homogenization of Nanoparticulate Pharmaceutical Dispersions

Process analytics is an important part of designing quality into pharmaceutical products. This project evaluates ultrasound-based process analytical tools (PAT) in a homogenization process of nanoparticulate systems that are intended for oral administration.

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Keywords: Ultrasound; resonator technology, manufacturing, process analytics, pharmaceutical dispersions

Introduction

These days the pharmaceutical industry attempts to design quality into their products rather than relying only on final end-product testing. This concept of "Quality by Design" was coined by the Food and Drug Administration (FDA) and should be implemented in pharmaceutical product development. A first step for pharmaceutical companies is to identify which material and process factors are critical to the relevant quality attributes. Such critical material/process variables should then be monitored. However this requires adequate process analytical technology (PAT). Much research has been dedicated to PAT and as a result of these efforts, several new sensor techniques have been successfully applied in pharmaceutics. The use of such techniques in development mainly targets better process understanding. On the other hand, PAT in production aims to reduce manufacturing failures and can help to cope with the variability of raw materials whilst still obtaining final product quality that is reproducible. While the majority of process analytical technology (PAT) focused on solid dosage forms or biopharmaceuticals, there was only limited work dedicated to studying pharmaceutical dispersions. Spectroscopic tools such as dispersive Raman sensors were used, as well as different techniques for particle characterization, e.g. the focused beam reflectance measurement.These tools may be used for diluted suspensions or emulsions but process analytics in turbid or concentrated dispersions remains a challenge. It was Medendorp et al. [1] who pioneered using acoustic resonance spectroscopy as a PAT tool in semisolid formulations. We were interested in a similar technique called ultrasonic resonator technology (URT). One of our projects employed this ultrasound technique to monitor drug concentrations in self-emulsifying drug delivery systems [2].

For the current project, we focused on the mixing of pharmaceutical solids and liquids to manufacture dispersions under high shear in a vacuum. For the initial feasibility study we first selected pharmaceutical nanosuspensions. Another aim of this project was to evaluate combinations of process analyzers. Since ultrasound analysis is very sensitive to density changes, we aimed to combine ultrasound measurement with a flow-through Coriolis force sensor.

Results

A series of suspension vehicles were investigated using ultrasonic resonator technology (URT). For the initial feasibility study, the samples (170 µL) were removed from the process stream, which is called at-line sampling. Fig. 1 shows how samples were collected from different positions within the mixing and homogenization vessel (Mi-Molto, Krieger AG).

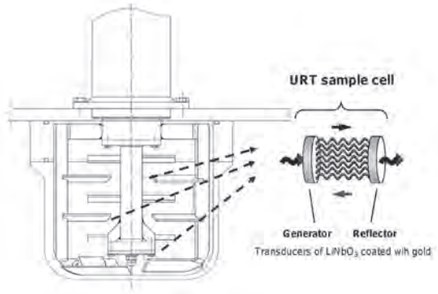

Figure 1 *Homogenizing vessel with sampling locations for the subsequent at-line analysis using ultrasonic resonator technology (URT)*

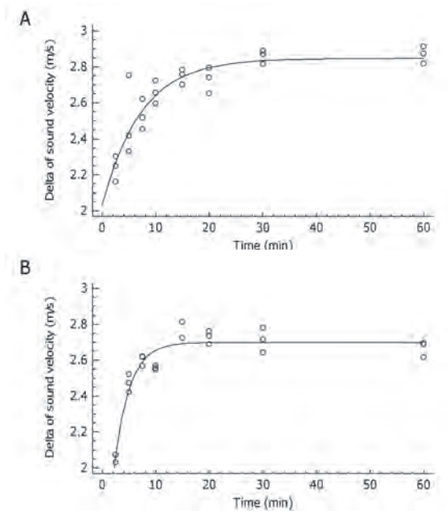

Figure 2 *Delta of ultrasound velocity (m/s) during homogenization of colloidal microcrystalline cellulose (bubbles). (A) First and (B) second batch are shown together with the model according to Eq. 1 (solid line)*

We measured the ultrasound velocity relative to a reference cell filled with water. A resonance frequency of 7-9 MHz at 25 ± 0.01°C was selected by the URT system (ResoScan®, TF Instruments Inc). The obtained delta of sound velocity, ΔU changed in the course of the mixing and homogenization process. A first model system was made of nanoparticulate microcrystalline cellulose with sodium carboxymethylcellulose (Vivapur MCG® 591PCG, JRS Pharma GmbH). A total concentration of 1.6% (w/w) was selected with 25 rpm stirring and 500 rpm homogenization speed. Fig. 2 displays the results of the measured change in ΔU as a function of the process time. As expected, the values initially increased and then gradually levelled off once the process reached its equilibrium. Such equilibrium itself was a remarkable finding as it indicated a balanced shear of the homogenizer so that the nanoparticulate gel-structure was not harmed by rather long homogenization and stirring times. The heuristic equation 1 was fitted to the experimental data:

$$\Delta U = \Delta U_{\cap} + s(1 - e^{-k \cdot t}) \quad (1)$$

The value ΔU_0 is the relative ultrasound velocity at the start of the homogenization process, whereas s and k are constants. The parameter s holds for the change from a ΔU_0 to a maximal value at the end of the process. Moreover, the parameter k can be linked to a half-homogenization time $t_h = \ln(2)/k$ as well as an equilibrium time $t_e \cong 4t_h$. This concept of a half-homogenization time was of special pharmaceutical interest, as it described the individual manufacturing kinetics of a given suspension. Based on such monitoring, the batch-to-batch variability was studied as well as the required process time.

Further aqueous and non-aqueous nanosuspensions were studied; for example Fig. 3 shows a clay-dispersion with xanthan gum (Vanzan NF 0.5% w/w) at 50 rpm stirring and 3000 rpm homogenization speed. Here, $-\Delta U$ was analyzed in the course of manufacturing. More results of the feasibility study can be inferred from an article in the Journal of Pharmaceutical Sciences [3] It was particularly interesting to note that acoustic attenuation (another parameter obtained from URT) was found to be even more sensitive compared to the delta of sound velocity. Both acoustic parameters are complementary and were successfully correlated with rheological properties of the formulations manufactured.

A next step in the project was to develop an on-line monitoring system. The company TF –instruments provided a prototype flow-through cell that was coupled with a piston pump to continuously draw samples from the manufacturing vessel. It was found that a rinsing of the cells in combination with "stop-flow" was needed for adequate on-line measurements. First suspensions and nanoemulsions were successfully measured using this PAT- equipment. It was further possible to couple a MEMS-chip based Coriolis force detector (Endress & Hauser AG) for continuous density monitoring of the model formulations. Additional modifications of the manufacturing vessel are currently being evaluated to obtain prototype manufacturing equipment.

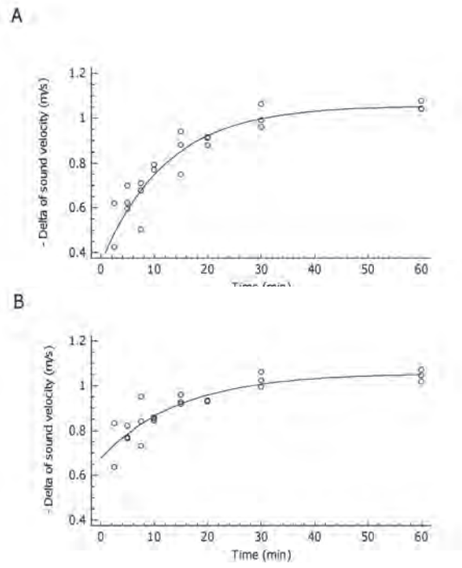

Figure 3 *Delta of ultrasound velocity (m/s) -delta U of the clay/xanthan system as a function of the homogenization time (bubbles). (A) First and (B) second batch are shown together with the model according to Eq. 1 (solid line)*

Conclusion and Outlook

The feasibility study indicated the usefulness of ultrasonic resonator technology as a PAT tool for pharmaceutical dispersions. First, at-line sampling was employed and in a second step, an on-line PAT version was developed. The technology can help in the development of pharmaceutical dispersions. The phase of process development in particular can profit from direct monitoring of the different ultrasound properties. However, the new technology also seems highly promising on the manufacturing level. A production environment often has to cope with the natural variability of raw materials. The ultrasound-based analytics can assess batch-to-batch variability and process times can be optimized for the individual product. A shortening of process times may lead to substantial cost savings in production. Further research will explore additional options to couple different sensors with the ultrasonic resonator technique.

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Funding:
Co-financed by Commission for Technology and Innovation (CTI)

Economic efficiency and benefit to society:

A first benefit is given for the industrial partner who is active in the machine manufacturing industry. Moreover, the new manufacturing equipment will provide better process understanding and fewer failures in pharmaceutical production. This and the potential reduction of process times are benefits for the pharmaceutical industry.

Determination of Degradation and Saturation Solubility of an Unstable Phytopharmaceutical Compound

One important step in drug development is assuring the bioavailability of an active compound. For this reason, physiochemical properties such as stability and solubility, which are essential for absorption, have to be determined. This is essential for understanding and improving bioavailability and hence enhancing the success of drug development.

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Keywords: Stability, solubility, kinetic model, lipid vehicles, phytopharmaceutical compound

Introduction

Knowledge of stability and solubility of the drug in different vehicles is required for absorption studies with the in vitro Caco-2 cell culture model. Such studies are carried out using in the apical compartment aqueous solutions or biorelevant media simulating the contents of the intestine under fasted and fed conditions [1]. In the experimental design with the biorelevant media, liposomal dispersions that are well tolerated by the cells are used in the basal compartment in order to guarantee cell viability. Chemical stability of the compound in these different vehicles can be measured at concentrations below saturation. Direct measurement of solubility at equilibrium in a saturated solution is not possible however, because of the fast degradation that takes place. The aim of this study was to investigate the degradation of the phytopharmaceutical compound Nobilin that is unstable in water and to develop a kinetic model for determining its saturation solubility in different vehicles.

Materials and Methods

Nobilin is a sesquiterpene lactone isolated from the flowers of Anthemis nobilis L. that was used as a model compound. Aqueous media (aq-TM_{caco}), fasted state simulated intestinal fluid (FaSSIF-TM_{caco}), fed state simulated intestinal fluid (FeSSIF-TM_{caco}), and two liposomal formulations in aq-TM_{caco} with the same lipid concentrations as FaSSIF-TM_{caco} and FeSSIF-TM_{caco}, respectively, were used as vehicles in stability and solubility studies.

Stability

The degradation was observed for 5-7 hours and was described by first order kinetics.

$$C(t) = C(0) \cdot e^{-k_d t} \quad (1)$$

where, C(t) and C(0) is the concentration at time points t and 0 respectively and k_d is the degradation constant.
The observed degradation products were analyzed by LC-MS.

Solubility

Nobilin was added in excess to the vehicle and the change in concentration of dissolved drug was monitored for 7-7.5 hours. The data were evaluated with a kinetic model by EASY-FIT® fitting software. The least square-based regression analysis provided an estimate of solubility.

Results

Stability

The degradation constant decreased in FaSSIF-TM_{caco}, FeSSIF-TM_{caco}, FaSSIF-TM_{caco}-Liposomes, and FeSSIF-TM_{caco}-Liposomes 1.3-fold, 8.6-fold, 8.7-fold, and 44.6-fold respectively compared to aq-TM_{caco}, whereas the half-life increased (Table 1).

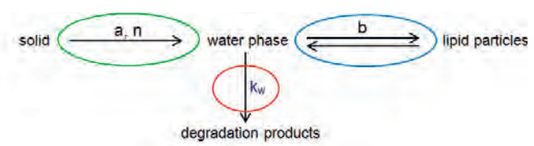
Vehicle Total lipid concentration [mM] Particle size [nm]	k_d [h^{-1}] Nobilin conc. [µg/ml]	$t_{1/2}$ [h]	C_s [µg/ml]
aq-TM_{caco} - -	0.4198 46.8	1.6	106.6 (± 4.3)
FaSSIF-TM_{caco} 3.2 83.2	0.3198 55.1	2.2	151.8 (± 13.4)
FeSSIF-TM_{caco} 17.8 68.8	0.0485 59.1	14.3	595.1 (± 29.5)
FaSSIF-TM_{caco}-Liposomes 3.2 120.7	0.0481 2.7	14.4	175.1 (± 10.1)
FeSSIF-TM_{caco}-Liposomes 17.8 124.9	0.0094 2.7	73.7	1077.6 (± 43.9)

Table 1 *Degradation constant, half-life of degradation and solubility of Nobilin in different vehicles.*

Five degradation products of Nobilin were detected by LC-MS. The determined molecular mass of degradation products a, b, and c was m/z=387.2 compared to m/z=369.2 of Nobilin, suggesting a water addition possibly in the double bond at positions 1, 4 and 11, or the hydrolysis of the lactone ring. The degradation product d (m/z=369.2) could be an isomer of Nobilin and e (m/z=351.2) probably results from loss of the hydroxyl group at position 3 (Fig. 1). The m/z of Nobilin and the degradation products correspond to the Na^+ adduct of the molecules.

Solubility

To calculate the solubility, a kinetic model was developed which included the dissolution rate (green), the degradation rate (red) and the transfer rate in and out of lipid particles (blue) (Scheme 1).



Scheme 1 *Kinetic model including the dissolution rate (green), the degradation rate (red) and the transfer rate in and out of lipid particles (blue).*

The change of the concentration in the water phase was expressed with Equation 2:

$$\frac{dC_w}{dt} = a \cdot t^n \frac{(C_s - C_w)}{V_w} - k_w \cdot C_w \pm b \frac{(C_l - C_w)}{\phi_w} \quad (2)$$

where, C_s is the saturation solubility, C_w is concentration in the water phase, C_l is concentration in the lipid particles, V_w is the volume of the water phase, ϕ_w is the phase fraction of the water phase, b is a transfer coefficient, k_w is the degradation constant in the water phase (0.4198 h^{-1} in aq-TM_{caco}), and t is time. The dissolution coefficient included the shrinking of the surface area of the particles as a function of time and was expressed with a power law,

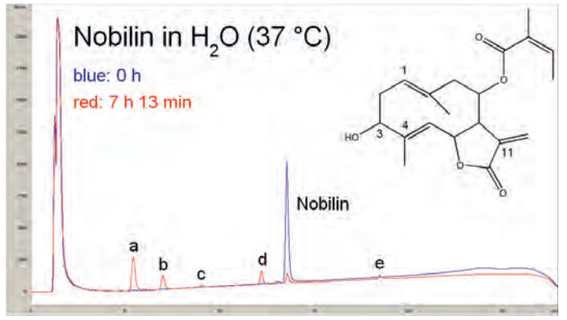


Figure 1 *Chemical structure and chromatograms of Nobilin and its degradation products at time point 0 and 7 h 13 min in water (37 °C).*

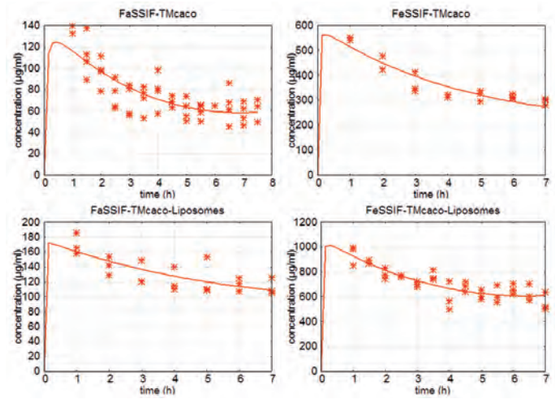


Figure 2 *(*) represent the measured concentrations of Nobilin in solution of four different vehicles as a function of time. The line (-) is the fitted model curve.*

$$\frac{D}{h} \cdot S(t) = a \cdot t^n \quad (3)$$

D being the diffusion coefficient, h the diffusion boundary layer thickness, S the surface area, *a* denoting a dissolution factor and n being equal to -1.14.

The total concentration, C_{tot}, was given by the following equation.

$$C_{tot} = C_w \cdot \phi_w + C_l \cdot \phi_l \quad (4)$$

C_{tot} corresponds to the experimentally determined concentration. The system of Equations 2 and 4 was fitted to the data (Fig. 2).

Table 1 shows the deduced solubility values. Solubility in FaSSIF-TM_{caco}, FeSSIF-TM_{caco}, FaSSIF-TM_{caco}-Liposomes and FeSSIF-TM_{caco}-Liposomes increased 1.4, 5.6, 1.6, and 10.1-fold respectively, compared to aq-TM_{caco}.

Conclusion and Outlook

The vehicles considerably increased stability and solubility of Nobilin to an extent depending on the drug-to-lipid ratio. The calculated logP of Nobilin is 2.572 (±0.601) [2] which suggests an encapsulation of the drug in colloidal lipid particles. This effect solubilizes Nobilin increasing its equilibrium solubility, and protects it from water addition, thus improving its stability. Furthermore, it seems that the structure of the particle plays an additional role. The liposomes increased stability and solubility of the compound more than the mixed micelles of the biorelevant media, even though their concentrations were the same. There are several examples in the literature which show that the addition of surfactant increases the stability and solubility of a drug. It was seen that penicillins were stabilized by cationic and nonionic micelles in acid solutions which prevent acid-catalyzed degradation. It was assumed that this stabilization was because of the lipophilic character of the compounds which led to incorporation into the micelles. This effect also increased solubility in the presence of nonionic micelles [2].
The mathematical model developed in this study allowed the calculation of the solubility of a compound while fast degradation and transfer in and out of lipid particles took place. Hence, this model can be a useful tool in drug development for estimating saturation solubility of an unstable drug. Interestingly, the model envisages that the dissolving drug first enters the water phase before transferring into the lipid particles. Assuming a direct transfer of drug from the solid state into the lipid particles did not provide a satisfactory description of the experimental data. It should be further noted that the transfer coefficient, b, could not be deduced because drug concentration in the water phase and the lipid particles, C_w and C_l respectively, was not known. The understanding of Nobilin interaction with the vehicles is very important for future absorption studies with the Caco-2 cell model and the calculation of permeability coefficients. It also provides insights into the possible improvement of bioavailability under biorelevant fasted and fed conditions.

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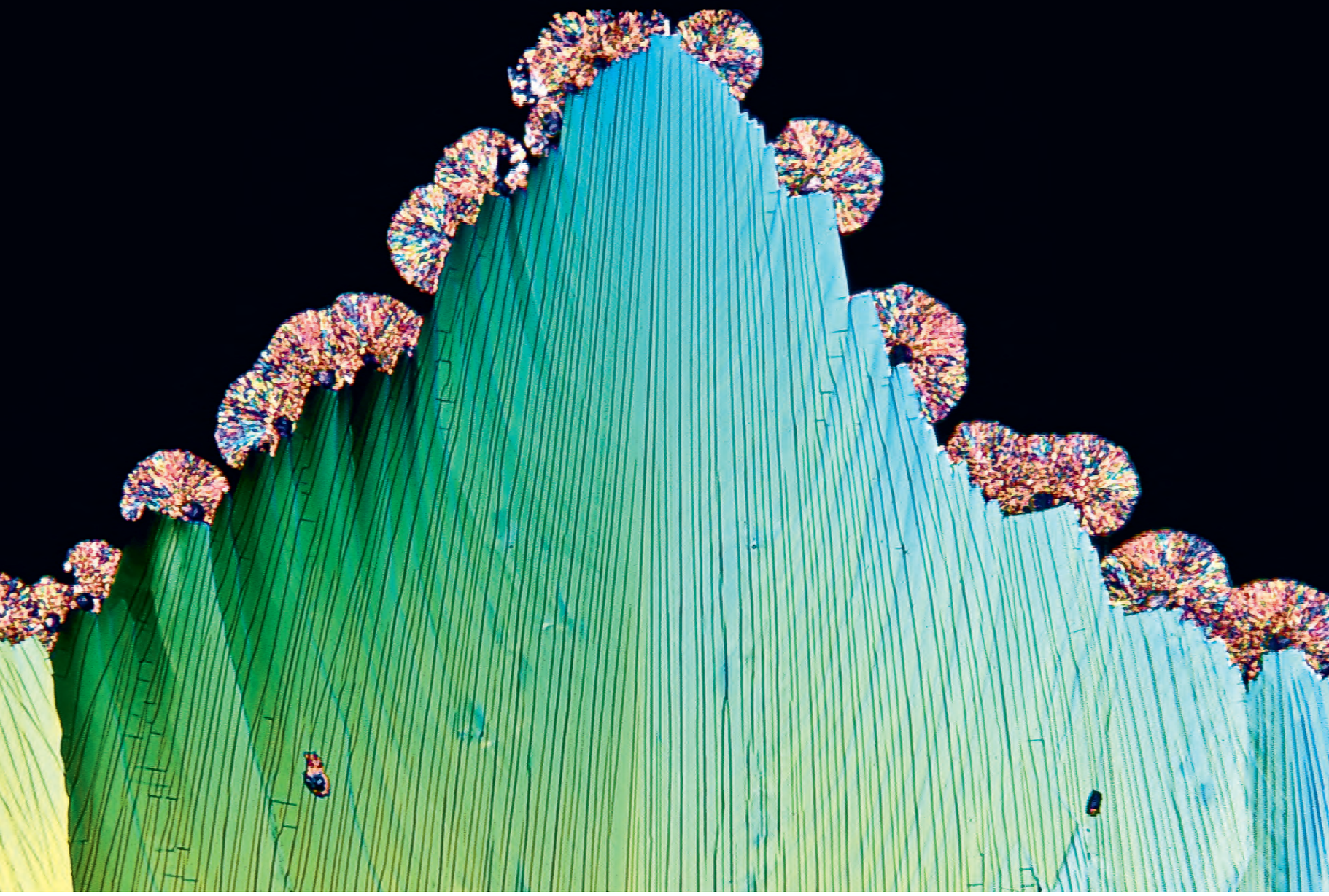
Alpinia Laudanum Institute of Phytopharmaceutical Sciences AG
Economic efficiency and benefit to society:
Knowledge of stability and solubility are crucial for absorption studies in order to improve bioavailability. Therefore a model which can help to determine the solubility of a highly unstable drug is a very useful tool in the development of drugs.



Environmental Technologies (ET)

Technologies and management for the sustainable use of resources and the preservation of the environment

Environmental Risk Assessment of UV-Filters

UV-absorbing chemicals (UV-filters) are increasingly used in sunscreens, personal care products (cosmetics) and in the protection of materials against harmful UV-irradiation. They enter the aquatic environment, where contamination occurs in waters influenced by wastewater. In previous projects, we have shown that some of these UV-filters have hormonal activities in fish.

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Keywords: Environmental Risk Assessment, UV-filters, Fish, Effects on hormone system

Introduction

Excess UV-radiation may lead to skin irritation and in the long-term, to skin cancer in humans. Materials are also negatively affected. To prevent exposure to increased UV-radiation, UV-absorbing organic chemicals (UV-filters) and inorganic nanoparticles (titanium dioxide, zinc oxide) that scatter UV-radiation are employed in sunscreens and material protection. With increased sun protection factors and in particular with the inclusion of UV-filters in all sorts of cosmetics, the use of organic UV-filters is steadily increasing. Some of these UV-filters have critical properties including high lipid solubility and persistence in the body and the environment. They enter the aquatic environment, where contamination is found to be widespread [1]. We show that some UV-filters have hormonal activities *in vitro* and affect fertility and reproduction in fish [2]. In fathead minnows (*Pimephales promelas*), estrogenic 3-benzylidene camphor and benzophenone-2 cause feminization of male fish, alteration of gonads, and a decrease in fertility and reproduction. We demonstrate that UV-filter mixtures act mainly synergistically *in vitro*, and have additive effects in vivo [2]. In addition to effects on the sex hormone system, inhibition of enzymes involved in the thyroid and glucocorticoid system may occur. At present it is unknown what kinds of gene or gene clusters related to hormone systems or physiological functions are affected by UV-filters. The aim of the ongoing research project is to deepen our understanding and further investigate the ecotoxicological effects of UV-filters. We focus in more detail on open questions on the molecular, biochemical and reproductive effects of UV-filters in zebrafish (*Danio rerio*). By means of transcriptomics, molecular effects on the whole genome of zebrafish are assessed. Specifically, we elucidate molecular effects of the UV-filters benzophenone-4 (BP-4), benzophenone-3 (BP-3) and ethyl-hexyl-methoxy-cinnamate (EHMC) on molecular pathways. Furthermore, adverse effects on fertility and reproduction in zebrafish are analysed. Overall, these studies are aimed at understanding the ecotoxicological effects of UV-filters, elucidating the modes of action, and contributing to the hazard and risk assessment of these widely used personal care products.

Results

In zebrafish embryos and adult males exposed to concentrations of **BP-4** between 30 and 3000 µg/L, for 3 days after hatching and for 14 days respectively, several genes belonging to the hormonal systems are altered [3]. They include steroid hormone receptors and genes coding for enzymes involved in the endogenous synthesis of steroid hormones (Fig. 1). In embryos, transcripts *of vtg1, vtg3, esr1, esr2b, hsd17ß3, cyp19b cyp19a, hhex* and *pax8* are induced at 3000 µg/L BP-4, which points to a low estrogenic activity and interference with early thyroid development respectively. In adult males, BP-4 displays multiple effects on gene expression in different tissues. In the liver, *vtg1, vtg3, esr1* and *esr2b* transcripts are down-regulated, while in the brain, *vtg1, vtg3* and *cyp19b* transcripts are up-regulated. The transcription profile reveals that BP-4 interferes with the expression of genes involved in hormonal pathways and steroid hormone synthesis. The effects of BP-4 differ in life stages and adult tissues and point to estrogenic activity in eleuthero-embryos and the adult brain, and antiestrogenic activity in the liver.

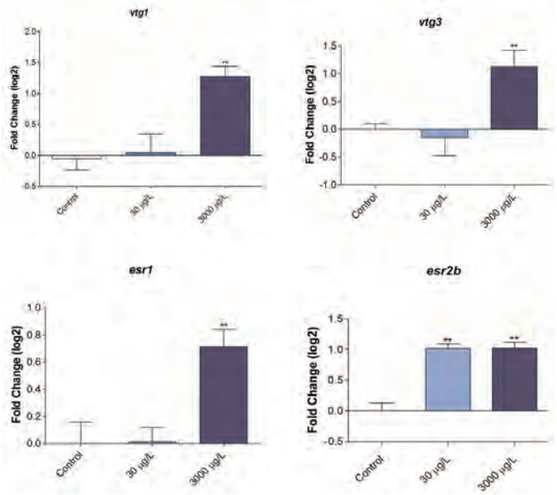

Figure 1 *Relative gene expression of vtg1 (A) vtg3 (B), esr1 (C) and esr2b (D). mRNA levels in zebrafish eleuthero-embryos after exposure to 30 and 3000 µg/L of BP-4. Relative transcript abundance was quantified by real-time reverse transcription PCR; the fold changes (log2) in vtg1, vtg3, esr1, and esr2b mRNA abundance as compared to control values were determined using 2–ΔΔCT method. Results are given as the mean value ± standard deviation (n=6 replicates for eleuthero-embryos). Asterisks indicate significantly higher expression than control (**p<0.01).*

Furthermore, effects of **BP-3** are evaluated in embryos and adult zebrafish that were exposed for 120 hours post fertilization and 14 days, respectively to 2.4–312 µg/L and 8.2–438 µg/L BP-3 (Fig. 2) [4]. Chemical analysis of water and fish demonstrates that BP-3 is partly transformed into benzophenone-1 (BP-1) and both compounds are accumulated in adult fish. Biotransformation into BP-1 is absent in eleuthero-embryos. BP-3 exposure leads to similar alterations of gene expression in both adult fish and eleuthero-embryos. In the brain of adult males *esr1, ar* and *cyp19b* are down-regulated at 84 µg/L BP-3. There is no induction of vitellogenin expression by BP-3, either at the transcriptional or protein level. An overall down-regulation of the *hsd3b, hsd17b3, hsd11b2* and *cyp11b2* transcripts is observed in the testes, suggesting antiandrogenic activity. Whole genome transcriptome analysis shows that 118 transcripts of different genes belonging to different biological functions are altered after exposure to 312 µg/L BP-3. No histological changes were observed in the testes after BP-3 treatment. Thus low concentrations of BP-3 exhibit similar multiple hormonal activities at the transcription level in two different life stages of zebrafish. Forthcoming studies should show whether this translates to additional physiological effects.

The UV-filter **EHMC** is heavily used in sunscreens and cosmetics and potential adverse effects or modes of action have not been investigated. We evaluate potential effects in another fish species, the fathead minnow (*Pimephales promelas*) [5], analysing the effects at measured water concentrations of 5.4, 37.5, 244.5 and 394 µg/L EHMC on the expression of genes involved in hormonal pathways in the liver, testis and brain of male and female fish. We compare the transcription profile with the plasma vitellogenin (VTG) content, secondary sex characteristics, and gonad histology. Transcripts of the androgen receptor (*ar*) are significantly down-regulated in the liver of females at 37.5 µg/L and higher. Additionally, the 3 β-hydroxysteroid dehydrogenase (3β-*hsd*) transcript is significantly decreased in the liver at these concentrations. The expressional changes are tissue-specific in most cases, being most significant in the liver. Vitellogenin plasma concentration increased significantly at 244.5 µg/L EHMC in males. EHMC also induces significant histological changes in testes and ovaries at 394 µg/L. The induction of VTG plasma concentration and the histological changes in gonads suggest an estrogenic and/or antiandrogenic activity of EHMC. On the other hand, the gene expression profile shows an antiestrogenic (e.g.:down- regulation of *esr1*) activity of EHMC. Whole-genome transcriptome analysis revealed that over 1000 transcripts of genes involved in diverse biological and physiological functions are altered. In conclusion, our data demonstrate that EHMC displays low but multiple hormonal activities in fish.

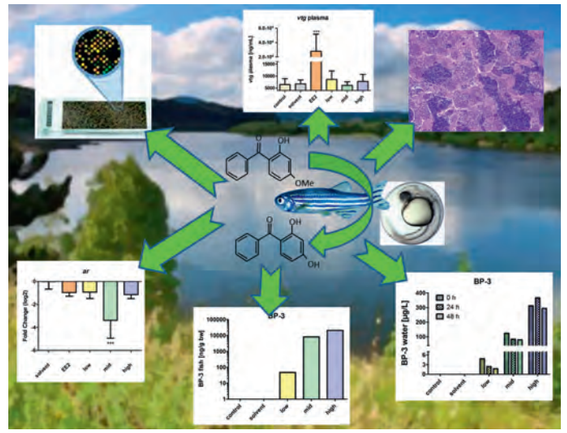

Figure 2 *Summary of methods used for investigation of effects of the UV-filter benzophenone-3 (BP-3) in adult zebrafish males and embryos. Chemical analysis comprised of exposure water and exposed fish analysis, showing that BP-3 is partly transformed to BP-1 in adults. The altered gene expression was studied using cDNA-microarrays and qRT-PCR and confirmed by vitellogenin protein analysis and gonad histology.*

Conclusion and Outlook

Our data indicate that the UV-filters BP-4, BP-3 and EHMC alter the expression of genes involved in hormonal pathways, hormonal signalling and in the synthesis of steroid hormones. Alterations of gene transcription occur in adult fish and in embryos, which may ultimately influence the development of gonads and the brain. The transcriptional changes in adult fish may lead to an imbalance of sex hormones, alterations in the gonads, as in the case of EHMC, and possibly to alteration of fertility and reproduction. Our data on several UV-filters clearly show hormonal effects in fish. However, these occur mostly at concentrations higher than those found in the environment. On the other hand, for other UV-filters we have previously shown that the effects of individual compounds are additive and may cumulatively lead to unwanted adverse effects of these cosmetic ingredients. Therefore, further research is needed to pin down the potential environmental risks of these frequently used chemicals.

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Research Focus Area:
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Swiss National Science Foundation (SNSF) and Federal Office for the Environment (FOEN)

Economic efficiency and benefit to society:

The results of this project allow the evaluation of potential environmental risks of UV-filters and help in reducing potential human and environmental health risks associated with widespread use by search for alternative UV-protection agents.

Sustainability, environmental fate and ecotoxic effects of organic photovoltaics

Organic photovoltaic solar cells are a promising new energy-delivering technology. Based on organic molecules, they are developed as an alternative to silicium-based solar cells because of their lightweight thin-layer structure, semitransparency and mechanical flexibility. Within the SUNFLOWER project, the environmental fate, ecotoxicological risks and sustainability aspects of this cutting-edge technology are investigated.

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Keywords: Organic photovoltaics, life cycle assessment, sustainability, environmental fate, ecotoxicity

Introduction

With fossil fuels dwindling, great efforts are currently being made to develop novel 'green' technologies in order to cover the ever-increasing worldwide demand for energy [1]. Organic photovoltaic solar cells (OPVs, see Fig. 1) are promising as a renewable energy source because of the low energy requirement for production, low resource extraction and absence of greenhouse gas emissions during use. In contrast to established silicium-based solar cells, OPVs have the advantages of light-weight, semitransparency and mechanical flexibility. In the SUNFLOWER project [2], funded by the European Commission, 16 academic and industrial partners are trying to develop new OPVs to improve their competitive efficiency and market price, as well as extend their lifetime to 20 years. Within the consortium, we focus on environmental aspects: in the context of possible large-scale production, the sustainability, environmental impact and ecotoxicological risks of OPVs are assessed and compared to the current best available technologies. Recommendations should be given to the industrial partners on how to make the production and disposal/recycling of such OPVs as eco-friendly as possible (see Fig. 2).

One target is to carry out a 'cradle to grave' Life Cycle Analysis (LCA) [3]. This means that from the extraction of raw materials, transportation, production of the OPV cell and its operation, until disposal or recycling, energy and material fluxes are determined to identify process steps which could be optimized.

Another objective is the investigation of environmental fate aspects [1]. The probability of a release of OPV components into the environment during the use and end-of-life phase of the OPV is assessed. Furthermore, it should be investigated whether such leaching compounds are bioavailable and can therefore be taken up by organisms in which they potentially cause toxic effects, whether they adsorb to organic material/soil or remain in water phase, and whether they are biodegraded under environmental conditions or by microorganisms.

The third purpose is to look into the ecotoxicological effects of OPV compounds [4]. A release of large concentrations of harmful substances under use-phase conditions is not expected but can potentially occur in the end-of-life phase. Whether or not a potential hazard for the environment from the different components used in OPVs (pure compounds as well as weathering products) exists, needs to be assessed by appropriate bioassays such as general toxicity and cellular stress responses.

Figure 1 *Semi-transparent OPVs have a good chance of success on the market for building integrated photovoltaics. [2]*

Results

The initial LCA and eco-efficiency assessment shows unique opportunities for a scenario of coating windows using transparent OPV in the large market of building integrated photovoltaics (see Fig. 3). In the reference OPV, produced by one of the project partners, the two electrodes consisting of transparent indium tin oxide (ITO) and silver are the main contributors to the environmental impact due to high energy consumption during production and uncertain environmental effects of ITO, which have not been investigated at all so far. Due to the high costs of scarce indium, replacement of ITO is an aim of the SUNFLOWER project. In addition to the replacement of ITO, emissions for OPV production could be reduced by using already existing renewable energies. Furthermore, the initial operational health and safety assessment revealed a lack of documentation for some materials, which should be further examined.

Concerning the fate and behaviour of OPV compounds in the environment, there is a general lack of information in literature about most of the main components. During use, when the OPV is in an intact state with almost impermeable barrier layers, the release of compounds into the environment

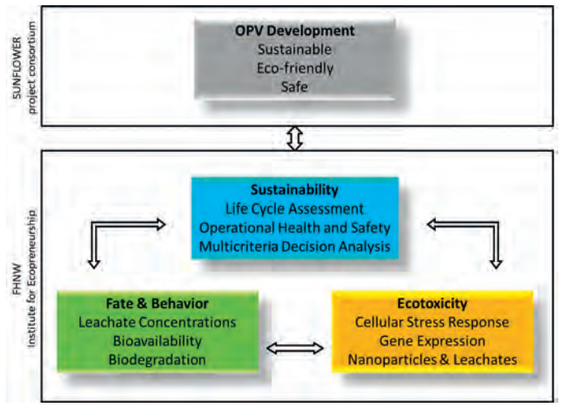

Figure 2 *A reliable environmental impact assessment for sustainable OPV will be provided to the SUNFLOWER project. (Y. Zimmermann)*

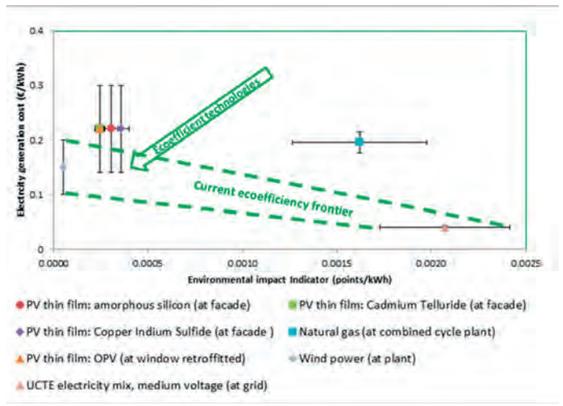

Figure 3 *The target is that OPVs cross the eco-efficiency frontier between clean wind energy and cheap UTCE electricity. (D. Hengevoss)*

is considered to be negligible. During the ageing process however, factors such as UV irradiation, water, oxygen, high surface temperatures and mechanical damage could lead to a release of OPV compounds. Initial results indeed confirm that metals may leach out of decomposed OPVs under harsh conditions such as cutting into pieces and agitating in artificial lake water. The extent, however, appears to be very low and metals are found only in trace concentrations in the tested leachate. Therefore, our preliminary data suggest that leaching of environmentally relevant concentrations of metals from OPVs might only occur under harsh conditions upon improper disposal in the end-of-life phase.

In toxicity tests, the potential effect of nanoparticles (e.g. ZnO) needs to be assessed. The biological activity of the pure chemicals/metals and leachates is analysed in fish cell systems (*in vitro*) and in early-life-stages of zebrafish (*in vivo*). Potential ecotoxicological activities are determined by biomarkers and targeted gene expression analysis. Different substance concentrations, from predicted environmental concentrations up to toxicological levels, will be tested. In a preliminary assessment, zebrafish embryos were exposed to nanoparticulate ZnO in media containing alginic acid as natural dispersant. First results demonstrate an induction of the oxidative stress marker gene catalase at high concentrations, but not apoptotic marker genes. In addition, the hatching rate was reduced. Overall, the preliminary results indicate a low ecotoxicological potential of nanoparticulate ZnO. However, further analyses are needed to assess the environmental safety of this and additional components of OPVs and leachates.

Conclusion and Outlook

So far, initial LCA shows that OPVs could have a considerable chance of success on the market with relatively low environmental impacts compared to other PV technologies. Assuming that the target of replacing ITO within the SUNFLOWER project will be achieved, the environmental impact of OPV will be further reduced. Concerning environmental fate aspects, until now there is no evidence for a worrying threat from OPVs since leaching concentrations are very low even under worst case scenarios. But since at present no policy/legislation and technologies regarding recycling of OPVs are in place, improper end-of-life disposal in particular might result in an adverse effect of OPVs in the environment, if applied on a large-scale. For ecotoxicity, in addition to single priority OPV components, tests using actual leachates (i.e. containing a cocktail of metals and organics) will be conducted using the developed set-ups. Here, biological activity will be analysed by applying an Effect Directed Analysis (EDA) based on the most promising bioassays.

In summary, our preliminary data indicate that OPVs can be considered to be a safe, eco-friendly and sustainable new technology.

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Research Focus Area:
Environmental Technologies (ET)

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Funding
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Economic efficiency and benefit to society
It is of high importance to gain insights into sustainability, environmental fate and ecotoxicological effects of the materials used already during OPV product development. In this manner, the production processes can be crucially influenced so that near-future, large-scale manufacturing of OPVs can be achieved with less environmental impact.

Advanced Concentrate Treatment for Integrated Membrane Based Water Reuse Systems

High quality water reuse with dense membranes is applied progressively but produces reject streams with elevated concentrations of organics and salts. This project aims to develop sustainable zero liquid discharge technologies allowing the application of dual membrane systems in inland locations. The main focus is on the behaviour and removal of bulk and trace organics to limit fouling and safeguard the quality of the water produced.

Christian Kazner and Thomas Wintgens
School of Life Sciences

Keywords: Water reuse, water scarcity mitigation, RO concentrate treatment, zero liquid discharge, environmental impact

Introduction

In the context of water scarcity mitigation, high quality water reuse based on dense membrane treatment is expected to be progressively applied to provide the additional water resources required. Environmental concerns and the high costs associated with membrane concentrate management limit however the application of high quality water reuse, especially in inland locations. The project investigates integrated reverse osmosis and nanofiltration membrane concentrate treatment concepts, with minimized costs and environmental impact. The volume of the concentrate streams typically ranges from 15 to 25% of the feed stream. High salinity, alongside the concentrated organic and inorganic toxic compounds, is a danger to many plants and animals. All available methods have serious shortcomings either from an environmental or an economic perspective [1].
Applying the sustainable Zero Liquid Discharge principle, the ACTIWATE project combines treatment methods for the removal of bulk and trace organics with a subsequent desalting system. The concentrate desalination will be based on a low energy consumption and low fouling concentration step, such as electrodialysis [2] or forward osmosis, thus increasing the salt concentration of the brine significantly in order to precipitate the salts; simple technologies such as wind aided intensified evaporation are used as a final stage for salt production. The system configuration, whether designed for reverse osmosis or nanofiltration concentrates, will differ due to different ion compositions. Instead of producing additional disposable waste, the salts should be recyclable. The focus of the research will be on the optimal removal of micropollutants and foulants affecting the desalting system to allow a complete recycling of the concentrate to the upstream process. Figure 1 provides a graphic illustration of the proposed integrated water treatment concepts. The technological activities will cover experimental and theoretical studies to investigate the most promising emerging concentrate treatment concepts and identify their technical feasibility, affordability and environmental sustainability. Feasible alternatives to organics removal and desalting processes with membranes, crystallization and energy-saving drying or separation processes will be evaluated.

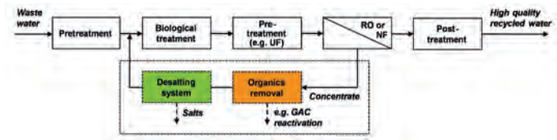

Figure 1 *Schematic of proposed integrated water reuse concepts for inland locations*

Results from the study on organics removal

Samples were taken and analysed from two advanced dual membrane water recycling plants in Sydney, Australia. The presence of organic micropollutants and bulk organics in relevant and typical concentrations was confirmed. The concentration of dissolved organic carbon was about 25 to 30 mg/L, mainly consisting of humic acids and building blocks. The main critical pharmaceuticals such as carbamazepine, diclofenac, and sulfamethoxazole were detected in the brine in concentrations of around 0.1 to 1 µg/L, using liquid chromatography with mass spectroscopy detection after enrichment of the target compounds by solid phase extraction.
The removal of organics can be achieved through a number of treatment technologies, e.g. ozonation, advanced oxidation processes, adsorption and biological treatment. Tests with granular activated carbon using rapid small-scale column tests with three different carbon types (two fresh carbons and one reactivated) revealed a rapid breakthrough of bulk organics after 2000 to 4000 bed volumes irrespective of the chosen carbon type. Trace organic compounds, however, were adsorbed to a significantly higher degree. Fresh mesoporous carbon was found to provide the best performance for the majority of micropollutants. Figure 2 illustrates the differences between typical compound classes based on key properties such as charge and hydrophobicity. Positively charged and neutral compounds were removed very stably, in particular by the fresh carbon. Negatively charged pharmaceuticals however started to break through after 5000 bed volumes. Besides compound charge, hydrophobicity seems to play the main role in adsorption as shown in figure 2 (log D at pH 7.5: diclofenac 0.74 compared to sulfamethoxazole - 1.51).

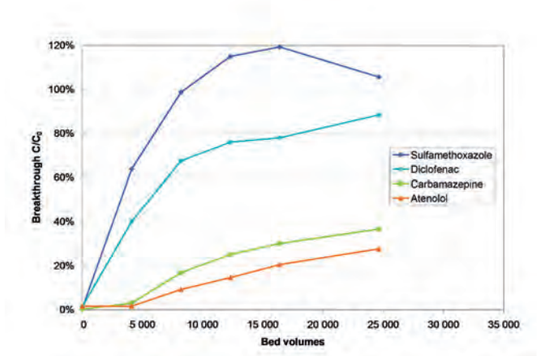

Figure 2 *Rapid small scale column test: Breakthrough of micropollutants*

Oxidative methods to partially break down bulk organics allow extending of the carbon usage. They appear to be advantageous, particularly in combination with biological activated carbon. A broad range of advanced oxidation methods and biological GAC have been tested earlier by [3, 4].

Results from the study on brine concentration

Electrodialysis (ED) and forward osmosis (FO) have been investigated regarding desalination performance and susceptibility to fouling. Both processes proved to be applicable for brine concentration when pH is properly controlled and the water is softened to avoid scaling by calcite. The tests for preferential process conditions are ongoing.
Fouling of ED and FO (cf. Fig. 3) was studied with model solutes containing humic acid, alginate and bovine serum albumin representing the key foulants: humic substances, polysaccharides and proteins. Tests with synthetic RO concentrate and model foulants were compared to tests with real RO concentrate. It was found that in FO fouling effects increased with flux, supporting the idea of a "critical flux". Two different membrane types were tested. The cellulose triacetate (CTA) membrane had a clean water flux around 12 LMH (draw solution 4M NaCl) whereas the novel polyamide (PA) membrane exhibited a clean water flux of 18 LMH (DS: 4M NaCl). When treating real RO concentrate for about 9 hours, the flux of PA membrane decreased by 30% whereas the CTA membrane lost only 15% in flux, indicating a significant influence of the membrane type and flux on FO fouling.

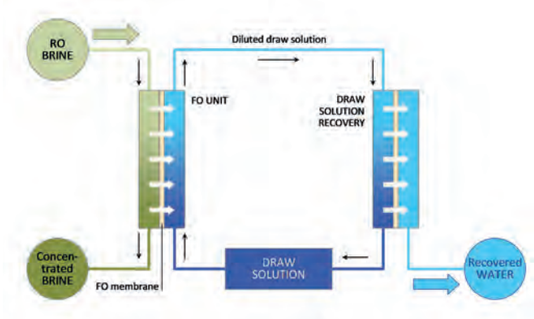

Figure 3 *Schematic of forward osmosis (FO) for RO concentrate treatment*

ED fouling tests revealed a strong impact of humic acids on the desalination performance by reducing the ion transport and increasing the energy demand. Counter ions such as calcium appear to play a key role in stabilisation of polysaccharides which were less fouling relevant than proteins and humics.

Conclusion and Outlook

Zero Liquid Discharge is gaining importance in the handling of municipal and industrial brine streams. Concentrates from water reclamation plants with dense membrane processes can be treated with a number of available and emerging treatment trains. The composition of reverse osmosis concentrates is complex and challenges the technologies for brine concentration such as forward osmosis or electrodialysis. Trace and bulk organics are present in elevated concentrations in reject streams from RO and NF up to 100 mg/L DOC. Organic compounds have to be removed prior to the concentration and desalting units to avoid severe fouling and performance loss of the desalting units. Combinations of oxidative and adsorptive processes appear to be most promising.

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Research Focus Area:
Environmental Technologies (ET)

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Partners
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Economic efficiency and benefit to society
Water scarce regions are currently at the point where substantial investment in inland recycling and advanced water treatment plants will be made. The project develops a new kind of high quality water reuse based on the principles of high water recovery and zero liquid discharge, minimizing liquid waste and environmental impacts.

Depolymerization of lignin by biocatalytic nano composites

The R&D project called DELICATE exploits the advantages of enzymes immobilized on nanomaterials for the biocatalytic depolymerization of lignin. Lignin modifying enzymes are immobilized on nanomaterials and membranes displaying re-generable activity. The immobilized multi-enzymatic complexes will be applied as a nano-biotechnology production process of lignin based biocomposite materials.

Gregor Hommes, Christoph Gasser, Erik Ammann, Melanie Mucha and Philippe Corvini

Keywords: Lignin, enzymes, membrane technology, fine chemicals

Introduction

Needs for alternatives concerning the production of chemicals from renewable materials

Dwindling stocks of fossil fuels and growing concerns over excessive emissions of greenhouse gases have forced researchers to investigate renewable, abundant and comparatively clean alternatives to liquid fuels and chemicals produced from petroleum. The option of replacing oil by biomass as raw material for both fuel and chemical production is of great interest. In so-called biorefineries, almost all types of biomass feedstock can be converted to different classes of biofuels, biochemicals or value added products through jointly applied conversion technologies. The biorefinery principle is currently gaining particular relevance for untapped or not sufficiently used resources such as biowaste or lignocellulosic material [1].

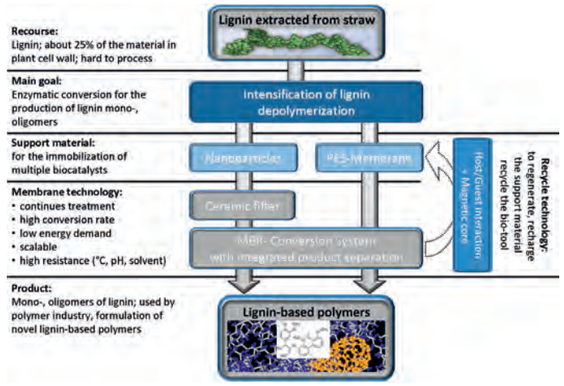

Figure 1 *Schematic overview of the project.*

Lignin as a relevant source for value added chemicals

Lignocellulosic biomass consists of three basic components: cellulose, hemicellulose and lignin. Most of the biorefinery schemes, however, focus on utilizing easily convertible fractions and hardly exploit lignin. For example, the lignocellulosics-to-ethanol process makes use of the cellulose and hemicelluloses, leaving lignin as waste. In addition, pulp and paper refineries also generate huge amounts of lignin as by-product. Lignin is, next to cellulose, the most abundant renewable resource. It is an amorphous and highly branched polymer of phenylpropyl units, accounting for up to 40% of the dry biomass weight. Presently, lignin is used as a low-grade boiler fuel to provide heat and power needed for the process. However, the chemical structure of lignin suggests it to be a good source of valuable chemicals if it could be broken into smaller molecular units. Several studies were carried out to convert lignin to more value-added products. The challenge, however, is that lignin is very difficult to decompose, leaving very high amounts of solid residue as compared to other components of lignocelluloses [2].

Aims of this study

The overall scientific goal of the present R&D project is to develop and apply a new biocatalytic nanomaterial-based process for the value-adding depolymerization of organosolv lignin extracted from straw and giant grass (Fig. 1). The biocatalysts, i.e. lignin modifying enzymes (LME) such as laccases and lignin peroxidase [4] are immobilized on the nanostructures of either magnetic fumed silica or ultrafiltration (UF) membranes. These materials are applied to eco-efficient (in terms of activity, stability and recyclability) membrane filtration-based processes operated in continuous mode for the production of lignin oligomers and monolignols with concomitant fractionation of the reaction products. The industrial relevance of these lignin depolymerization products is tested regarding their suitability as additives for the formulation of "green polymers" by the chemical industry.

Results

In order to reach the overall objective several intermediary objectives have to be met. The first step was to establish and apply a wide range of biochemical and physico-chemical analysis tools for the evaluation of the process performance. In this context we have achieved our first results.

Developing and establishing of analytical tools

Lignin as a macromolecular substance is very difficult to analyze with conventional analytical methods. For this reason a way had to be found to separate the macromolecules from the monomeric compounds of the process input material. Size exclusion chromatography was applied for a first separation based on molecular weight. Lignin, based on its origin, has a typical chromatographic fingerprint, due to the UV absorption of its different components (Fig. 2, left). The molecular weight distribution of Organosolve lignin lies in the range of ~0.1-50 kDa with an molecular weight-average of Mw = 1700 which is quite low compared to finger prints reported for lignin originating from other extraction procedures e.g. Kraft extraction with alkaline solutions.

Based on the characteristic fingerprint, modifications after enzymatic treatment can be followed as the specific UV absorption of the mono- and polymers will change. This is an important step for estimating the impact of the enzymatic treatment on the molecular weight distribution of lignin.

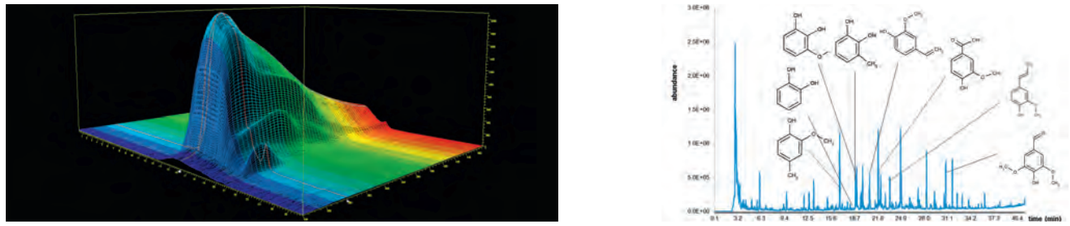

Figure 2 *Size exclusion chromatogram of organosolv lignin (3D absorption spectra from 240 - 470nm; left); organosolv lignin recorded after pyrolysis (920°C) and detected by GC/MS system; after thermolysis monomeric fragments of lignin are formed and their molecular structures can be determined via MS-fingerprints (right). (right).*

Another possibility to characterize the molecular structure of lignin and biotransformation products of lignin is analysis by pyrolysis-gas chromatography/mass spectrometry. Pyrolysis is the thermochemical decomposition of organic substances in an oxygen-free atmosphere. Through cracking of the macromolecular structures, a heterogeneous gas is formed containing molecules of lower molecular weight. These compounds can be separated by chromatography according to their polarity and vapor pressure (Fig. 2, right). Some of the resulting phenolic fragments are displayed in Figure 2, which are typical for lignin and derive from guaiacylpropanoid and syringylpropanoid lignin units, for example p-creosol, catechol, 3-methoxy-pyrocatechol, pyrocatechol, vinylguaiacol, 2,5-dimethylhydroquinone, vanillin and syringaldehyd (listed from left to right).

Magnetic Nanobiocatalyst

In order to facilitate the recycling and recovery of the biocatalyst, a second goal was to develop a magnetic nanobiocatalyst based on a recently published protocol [4]. The immobilization of an LME (i.e. laccase) resulted in magnetic nanoparticles bearing an enzymatic activity of 0.79 ± 0.02 U mg^{-1} (Fig. 3). In contrast, immobilization of the same enzyme on fumed silica nanoparticles yielded activities of 1.53 ± 0.02 U mg^{-1} fumed silica nanoparticles [4].

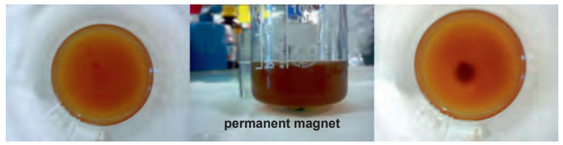

Figure 3 *Immobilization of LME onto magnetic silica-nanoparticles; from left to right migration of the magnetic nanoparticles forming a dark spot of where the magnet is located.*

Conclusion and Outlook

By developing and establishing thorough analytical methods for the characterization of lignin and lignin transformation products, essential tools for the evaluation of the tested conversion processes were obtained. Methods that allow identification of changes in the molecular weight distribution of lignin (i.e. SEC) are of particular interest for the identification of conversion processes which lead to lignin depolymerization. The enzyme immobilization technology has been transferred to INOFEA GmbH, which enables the company to produce nanobiocatalysts at large-scale.

Using magnetic nanobiocatalysts a separation technology can be developed to quickly and easily separate and recycle catalysts. Complex, multifunctional magnetic nanoparticle systems with designed active sites, i.e. LMEs, are promising candidates for the application in biocatalytic lignin conversion. The range of industrial applications which can be developed for such a system in the frame of DELICATE will depend on the possibility to further develop stable and robust magnetic nanoparticles withstanding the conditions encountered in the conversion process to effectively depolymerize lignin in an economical and scalable fashion.

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Research Focus Area:
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Partner:
Huntsman Advanced Materials (Switzerland) GmbH, Inofea GmbH, Eco-techniques SARL, MMS AG, Representa AG

Funding:
Commission for Technology and Innovation (CTI) and Partners (see above)

Economic efficiency and benefit to society

Decreasing society's dependence from petroleum is generally viewed as an important contribute to the development of a sustainable industrial society and the reduction of greenhouse gas emissions. Efficient valorization of lignin will contribute to the reduction of the price of biorefinery products (i.e. biofuel) since raw materials being responsible of almost half of the total production cost.

Comparing two Hybrid-Membrane-Processes to remove micropollutants from wastewater treatment plant effluent

Federal regulations for the removal of micropollutants from the effluent of wastewater treatment plants (WWTP) in Switzerland are expected to demand the upgrade of around 100 WWTP with an additional treatment step within the next 20 to 25 years. Within the project Aquapure the feasibility of two Hybrid Membrane Processes (HMP) is investigated and their performance is compared.

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Keywords: Tertiary wastewater treatment, powdered activated carbon, membrane filtration, Micropollutants

Introduction

The presence and accumulation of synthetic organic contaminants in ranges of µg/L to ng/L (micropollutants) in natural water bodies is a known phenomenon in industrial countries and a rising concern to efforts of protecting drinking water resources as well as the environment from negative human influences. The use of synthetic substances in household products, pharmaceuticals and pesticides is steadily increasing and their negative effect on marine environments has been demonstrated [1], [2]. The discharge of micropollutants through the effluent of wastewater treatment plants (WWTP) has been identified as one main entrance path into the natural water bodies [2], [3].
Serious efforts are underway in Switzerland to reduce the discharge of micropollutants into natural water bodies. Within the next 20 to 25 years around 100 of the currently operating WWTP are supposed to be upgraded with an additional treatment step to reduce the discharge of micropollutants, according to a proposed amendment of the Water Protection Ordinance (WPO) in 2009 [2], [3]. Not only in Switzerland but also in other industrialized countries within Europe efforts are taken to reduce the discharge of micropollutants [3].
Efforts to identify suitable and economically feasible process combinations have been a focus of environmental research in Switzerland as well as Germany over the last years. Powdered activated carbon (PAC) adsorption has been identified as one promising option [3].
Membrane filtration offers several advantages over other separation technologies such as sandfiltration or dissolved air flotation by completely retaining solids and PAC from the effluent, complete bacteria and partial virus removal and less space demand than alternative processes. The process combination of PAC adsorption and subsequent membrane filtration is referred to as Hybrid Membrane Process (HMP) and the working principle to remove micropollutants from an effluent stream is given in Figure 1.

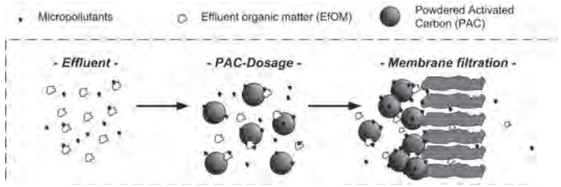

Figure 1 *Principle of micropollutant removal by Hybrid-Membrane-Processes*

Within the scope of this report, the comparison of two HMP applying PAC in combination with ultrafiltration (UF) to remove micropollutants from the effluent of a WWTP (ARA Birs, Basel-Land/Switzerland) is outlined. The HMP differ concerning the membrane process which is applied in combination with a PAC dosage of 20 mg/L. A pressurized membrane process as well as a submerged membrane process was operated in parallel on the same effluent stream and PAC dosage. The two membrane processes differ in various process conditions such as retention time of PAC, cleaning cycles and membrane material.
The experiments target to answer the question whether or not the HMP is a feasible option for the removal of micropollutants at the given location and water composition as well as which of the two systems promises better system performance. Criteria to determine the more efficient system were permeability of the membranes, maintenance demands, stability of the process, trace contaminant elimination, effluent water quality and material endurance.
The HMP is designed to be a tertiary treatment with PAC recirculation into the biological stage of the sewage plant in order to enhance micropollutant removal rates. The general process scheme of an HMP applied as tertiary treatment is given in Figure 2.

Figure 2 *Principle process scheme of a WWTP with additional HMP treatment*

The addition of PAC was performed at a target concentration of 20 mg/L which was found to be sufficient based on previous studies on PAC adsorption on WWTP effluent [4].
Within the project the removal of seven micropollutants were investigated namely Diclofenac, Sulfamethoxazole, Iopamidol, Carbamazepine, Mecoprop, Benzotriazole and Estrone.

Results

The membrane installations were operated at a constant flux for a certain filtration time and backwash was performed regularly. The systems were operated in parallel over a period of six months in 2011.
The comparison of the membrane systems showed a high recovery rate of around 80% and 90% for the submerged and pressurized systems respectively.
The good permeate quality achieved by the HMP was characterized by complete bacteria and partial virus removal as well as a removal of 50% of residual DOC compared to the WWTP effluent.

The investigation of the membrane surfaces after operation with PAC for the duration of half a year showed no membrane deterioration caused by PAC abrasion. The membrane surfaces were anayzed with an Environmental Scanning Electron Microscope EVO 40 (Carl Zeiss AG, Germany). Impressions of the membrane surface of both HMPs are shown below:

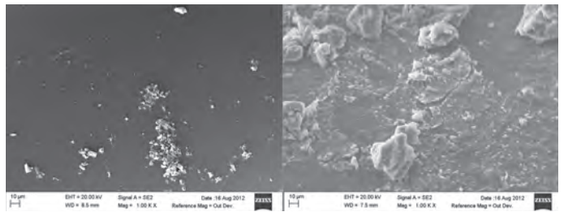

Figure 3 *Impression of the membrane surfaces.*

A thin layer of PAC was visible on the pressurized membrane surface (Fig. 3; left) while the membrane surface underneath appeared smooth and clean. The surface of the submerged membrane (Fig. 3; left) was covered by what is believed to be a combination of PAC particles as well as organic fouling. The different fouling layers on the membranes are an explanation for the difference in operational performance and are caused by the different process conditions.

In the period from the 8th of July until the 9th of August 2011 the removal of micropollutants from the wastewater treatment plant effluent was evaluated. The comparison of both HMPs concerning their capability to eliminate micropollutants from the WWTP effluent showed a removal in the range of 60-90% for most analyzed substances over the tertiary treatment step. Only Sufamethoxazole was removed to a lower degree due to its hydrophilicity.

Conclusion and Outlook

The comparison of both HMPs showed general feasibility of both systems to eliminate micropollutants from the WWTP effluent at stable operating conditions of the membrane processes. Retention for all analyzed substances was in the range of 60–90%, except for Sulfamthoxazole which adsorbed to a lower degree due to its high hydrophilicity and the comparably high DOC concentration during the sampling period. The high dependency of SMX adsorption onto PAK on the DOC concentration has been shown in different studies [5].

The pressurized membrane system showed particularly stable permeability values over the entire experimental period. The membrane performance increased slightly by the addition of PAC while the positive influence of 4 mg Fe3+/L as coagulation agent was significantly higher for the pressurized system.

Effluent water quality was improved by both HMPs by a DOC reduction of around 50% and complete bacteria and partial virus removal.

Both systems were operated for about 6 months and showed no damage to the membrane surface from PAC abrasion as observed with SEM. The stability of the membrane surface regarding abrasion caused by PAC is further supported by the biopolymer retention which remained stable during the experimental period (data not shown).

Further experiments are planned on a pilot scale to confirm the results of the small scale experiments.
It is assumed that in upcoming pilot scale experiments the PAC dosage will be achieved at much more stable conditions. The influence of the contact time of PAC and the elimination rate of the chosen micropollutants will be studied. Furthermore, the influence of two different PAC types will be investigated and the membrane process will be further optimized regarding its recovery rate and energy demand.

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WABAG Wassertechnik AG, Amt für Industrielle Betriebe Basel Land (AIB), Dolder AG
Funding:
Federal Office for the Environment (FOEN)
Economic efficiency and benefit to society:
Hybrid-Membrane-Processes are capable of improving the water quality of wastewater treatment plants to a high degree, by retention of bacteria and viruses as well as the removal of micropollutants to a high degree. This lowers the human impact on the environment.

Risk characterization of innovative bio-processes for water purification

New technologies may come with new risks. This is also true for environmental technologies aimed at reducing the pollution coming from contaminated sites or wastewater release. The MINOTAURUS (Microorganism and enzyme Immobilization: NOvel Techniques and Approaches for Upgraded Remediation of Underground- wastewater and Soil) project investigates such bioremediation technologies and aspires to undertake a proper risk characterization – at an early stage of technology development. To this end a a risk characterization approach is being adopted.

Claudia Niewersch, Olga Steiger, Christoph Hugi, Luca Antonozzi, Gregor Hommes, Rita Hochstrat, Thomas Wintgens
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Keywords: Risk assessment, risk characterization, International Risk Governance Council, bioremediation-processes

Introduction

Emerging technologies can be accompanied by risks for the environment, human health and safety. The MINOTAURUS project develops new bio-remediation processes aimed at reducing the emission of organic pollutants and by that lower the negative impact of these substances on the environment. The common principle of the new processes is the immobilization of biocatalysts; the negative impact of organic pollutants on the environment and humans will be reduced by these innovations. This paper presents a methodology to assess any additional or newly-occurring harmful effects of the innovative technologies. Since these effects are mainly connected to unusual events or failures in the operation of the new processes, the possible harm is described and assessed in terms of risks.

For this risk assessment the general framework of the International Risk Governance Council was used [1]; the structure and the main steps are shown in figure 1. The parts marked in red are the focus of the study presented in this paper.

Risk is understood as "an uncertain consequence of an event or activity with respect to something that humans value" [1, 2]. Risk assessment aims to estimate the frequency of occurrence of adverse effects as a function of the consequences of these adverse effects. Sources of adverse effects are often referred to as hazards. The exposure and vulnerability assessment considers the various pathways along which subjects of protection (e.g. groundwater, soil) might come into contact with hazards.

The complete framework aims to generate not only knowledge, in the form of information about and characterization of risks, but also measures to control those risks which were estimated to be not (fully) acceptable. The concept of risk governance has to be understood as a cyclical process: in the case of remediation technologies, the technology itself can already be seen as a risk reduction option.

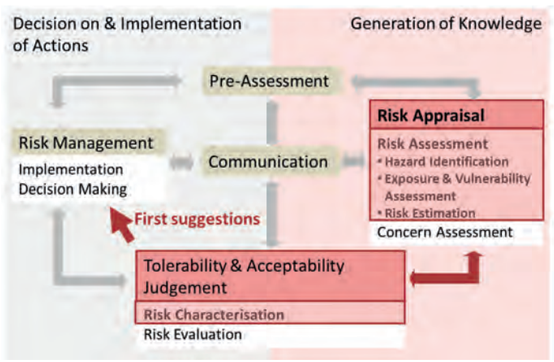

Figure 1 *Simplified Scheme of the risk governance framework (in red the focus of this paper) [adopted from [1]]*

Results

The new technology addressed here consists of a membrane reactor containing nanoparticles with immobilized enzymes. The pre-treatment, the production process of the nanoparticle-enzyme-conjugation, the required transport, the membrane reactor operation and the disposal of wastes were all taken into account in the assessment [3]. The new technology is still under development and naturally not much statistical data is yet available. Frequencies and consequences can therefore only be estimated in a semi-quantitative or qualitative way.

According to the high uncertainty of the results of the risk estimations, it is not possible to rely strongly on the calculated values as exact numbers for the total risk of the technology nor for individual risks. The benefit of this study is rather a comparison of the risk connected to different events and hazards. It is possible to set out a first prioritization of risk reduction measures, as well as a comparison of the shape of the risks in the consequence-frequency diagram.

The risk assessment at this stage of development of the technology is suitable for the identification of relevant events and hazards.

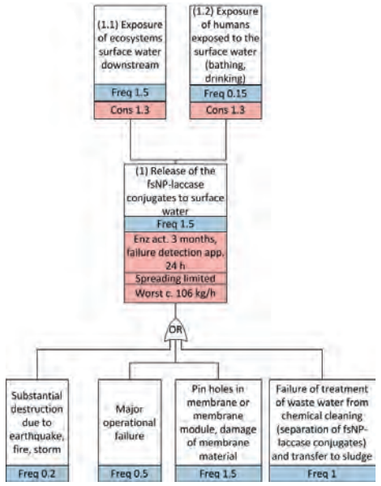

Figure 2 *Example for a combined fault-event-tree (blue boxes refer to frequencies, red boxes to consequences)*

The methodology applied here contains, as a first step, a systematic hazard identification based on the coarse risk analysis and the hazard and operability methods presented by Hokstad et al. [4]. This is done by structuring the whole process into suitable sub-processes. Each sub-process is then analyzed for relevant parameters and components, among which hazards are identified. The list of hazards is the basis of the vulnerability and exposure assessment using combined fault-event-trees according to the structure shown in Figure 2. The general idea of combining fault tree analysis with event tree analysis is meant to reduce the complexity of the fault tree and to increase the applicability to a real system. In a pure fault tree analysis the top or final undesired events are analyzed by developing causal relationships of events until arriving at the so-called basic events. The basic events are events for which the frequencies are sufficiently defined. In combination with event tree analysis, so-called intermediate undesired events are defined. For these the causal relationships of occurrence are developed in the form of a fault tree. Additionally, an event sequence is developed based on the intermediate undesired events [5].

In order to perform the risk estimation an analysis was done regarding frequency and consequence of the final events following the fault-event-tree structure. The estimation of the frequencies was done with a semi-quantitative scale: 0 (never happens); 1 (is expected to happen about once in 10 years); 2 (is expected to happen about once a year); 3 (always happening). The occurrence of events to be assessed was fitted into this scale. The consequences were qualitatively estimated using the following scale: 0 (no impact); 1 (minor impact); 2 (major impact); 3 (catastrophic impact).

Using this approach 24 fault-event-trees were developed including 19 different basic events in total. In order to generate useful data for a risk assessment study, the data from the lab and pilot scale experiments were extrapolated to a virtual full scale system, namely a large waste water treatment plant (WWTP) for 590,000 person equivalents. Two additional fault-event-trees reflect a baseline system which means the virtual full scale system without the new technology assessing the risks caused by the pollutants.

First results of the comparative risk assessment are shown in Figure 3 as a so-called loss exceedance frequency curve. This curve represents the frequency of events increasing the corresponding consequence given on the x-axis. It can be clearly observed that the shape of the loss exceedance curve changes significantly. For the situation that the technology is not applied, there are only risks with a very high frequency but with a relatively low consequence. The technology addresses micro pollutants which are continuously emitted from the WWTP at a low concentration leading to small effects, especially to aquatic ecosystems. If the technology is applied, risks with extremely high frequency are reduced significantly but new risks with low frequency but relatively high consequences are increased. Examples are the release of harmful chemicals by failure in the transport chain and membrane integrity failure.

Conclusion and Outlook

The results show that the risk assessment methodology helps to identify possible risks connected with a new technology systematically and at an early stage of development. Risk reduction options can hence already be taken into consideration before the first full scale installation.

During the future periods of the MINOTAURUS project it is planned that this methodology will be applied to further new biological remediation technology.

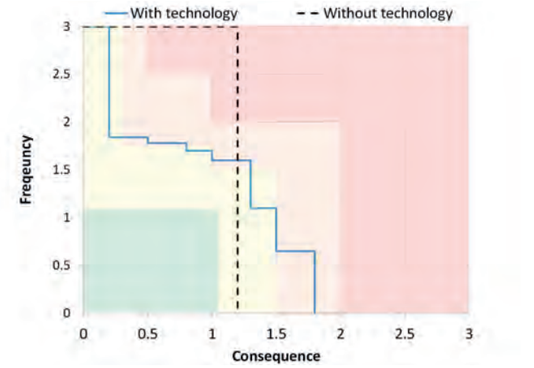

Figure 3 *Loss exceedance frequency curve comparing risk assessed for the application of the technology and risks occurring without the technology*

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Research Focus Area:
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Economic efficiency and benefit to society:
Performance of a risk characterization in the development phase of a new technology enables an early identification of risks and risk reduction options. As a consequence, risks for the society can be managed in more preventive way and the safety for the environment and the population can be improved.

EcoWater: Meso-level eco-efficiency indicators to assess technologies and their uptake in water use sectors

The EcoWater research project aims to develop meso-level eco-efficiency indicators for technology assessments using a system optimising approach, which is tested in case studies on different water service systems. The case studies in urban water systems are a first step where the water value chain was mapped and environmental and economic impact indicators were proposed.

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Keywords: Water resource management, eco-efficiency, meso-level, innovation and technology assessment

Introduction

Innovative techno-economic systems, able to decouple economic growth from resource use and depletion, are essential for a resource-constrained world. Significant research effort is dedicated to measuring progress towards this goal, focusing on improving eco-efficiency - the development of more economically valuable goods and services, while using fewer resources and generating less waste and pollution. Although eco-efficiency metrics are widely applied at the micro- and macro-levels, the corresponding indicators are not well suited to analysing systemic changes on a meso-level. Meso-level assessments, which focus on the dynamic behaviour of product and service systems, i.e. whole value chains, can be used to analyse interdependencies and heterogeneity among actors, and can thus support policies aimed at sustainable systems.

EcoWater seeks to address the existing gap in eco-efficiency metrics by adopting a system approach for developing meso-level indicators and for assessing the system-wide impact of innovative technologies. The approach is tested through case studies on water service - water user systems. The reasons for this are manifold. Water is a crucial life and production factor and causes significant environmental impacts and costs for sourcing, distribution, collection, and treatment. Further reasons are the need for holistic approaches in assessing the performance of different water-related innovative technologies and the fact that so far the uptake of innovations in the water sector remains primarily regulatory-driven.

Results

By studying the whole water value chains, as well as the interactions of the relevant actors, EcoWater will try to understand how technological changes in water service systems interrelate and influence the economic and environmental profile of water use in different sectors.

One of the research objectives of EcoWater includes the selection of eco-efficiency indicators, suitable for measuring the system-wide eco-efficiency improvements from innovative technologies. Eco-efficiency generally refers to a relationship between socio-economic benefits and environmental impacts (mainly negative) of a certain activity. Often this relationship is expressed as the ratio of an economic benefit and an environmental impact parameter. This ratio allows the comparison of system options, surveying development over time or even benchmarking with similar systems [1]. Such calculations often form the basis for improving the ratio between economic benefits and environmental impacts.

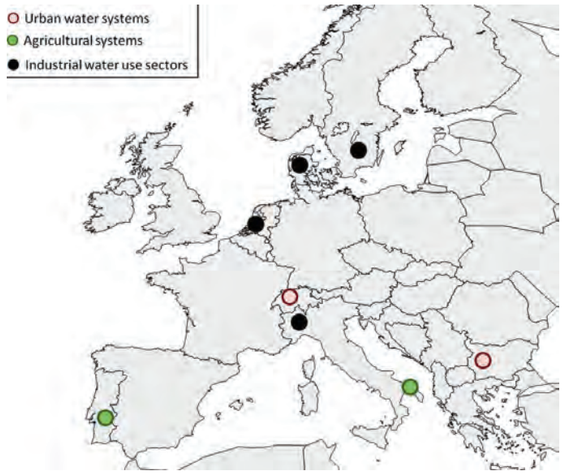

Figure 1 *FP7 EcoWater locations of case studies*

The challenge in EcoWater is the identification of suitable eco-efficiency indicators for the meso-level. The water sector is especially interesting for such investigations due to the heterogeneous actors and the interdependent system dynamics. For the main system components, i.e. the water supply, water use and the wastewater treatment system, different actors are relevant. These include political actors of different levels, operators for the water supply and wastewater treatment systems and industries, as well as small and medium enterprises and households in the water use system. In an interdependent system measures implemented in one component can result in positive or negative impacts in another component of the value chain. Furthermore, some measures might increase the eco-efficiency of the whole water system but are not implemented due to a prohibitive cost-benefit distribution. To overcome such a sub-optimal system configuration and foster the uptake of eco-efficient improvement technologies a framework for assessing technology impacts on the eco-efficiency of the whole water system will be developed by the project partners.

This framework development runs in parallel with, and at the same time is tested by, case studies, the elaboration of which is another research objective of the EcoWater project. These sample case studies are performed in a range of systems and sectors to assess innovative technologies and practices and to improve the understanding of the socio-technical dynamics that influence technology uptake and implementation in the water system. Two case studies are being undertaken by project partners in the agricultural sectors in Portugal and Italy and four in the industrial sector: one in the textile industry in Italy, one in the automotive industry in Sweden, one in the dairy sector in Denmark and one in energy production in the Netherlands (Fig. 1). We are work package leader for the case studies in urban water systems. One case study is being carried out in the Canton of Zurich (Waedenswil) and one in the city of Sofia, Bulgaria, in cooperation with the University of Architecture, Civil Engineering and Geodesy in Sofia.

For the Waedenswil urban case study we are closely cooperating and coordinating its activities with AWEL, the Office of Waste, Water, Energy and Air in Canton Zurich. So far, the whole water supply chain for the Waedenswil system has been mapped (Fig. 2) and the water system structured in three stages: water supply, water use and wastewater disposal. Within these three stages six nodes were selected for closer analysis and site visits were carried out to the Hirsacker and Appital drinking water treatment plants, four sample SMEs and the Waedenswil Rietliau wastewater treatment plant. There, water-relevant processes were investigated and data collected on water and resource flows, environmental issues related to water, and on costs and financial flows. With this data a value chain mapping of the system was drawn up, including relevant actors and stakeholders and the interactions among them (Fig. 3). In addition to the water flows, energy and financial flows were also mapped. As a next step the relevant environmental impact indicators and the economic benefits and costs for each actor in the system will be identified. Energy consumption and water contamination by micro-pollutants will be among the most relevant environmental impact indicators for this case study [2]. These indicators, combined with the associated benefits and costs, will give an indication of the eco-efficiency of the processes involved in the whole value chain, i.e. on a meso-level.

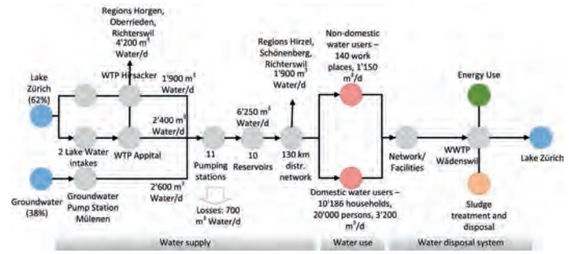

Figure 2 *Detailed mapping of EcoWater case study water system in Waedenswil (ZH)*

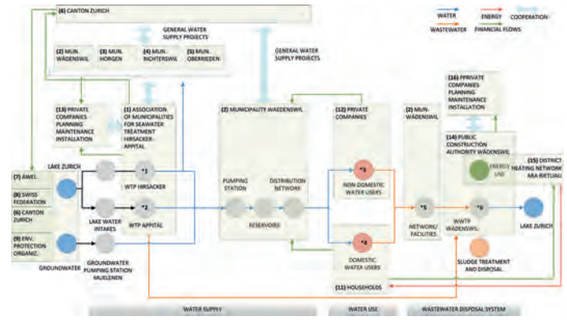

Figure 3 *Value chain mapping of Waedenswil water system*

Conclusion and Outlook

For the case study in Waedenswil the detailed value chain mapping has been completed. A range of indicators will now be tested to calculate different eco-efficiency ratios of the current water service systems and innovative technologies able to improve the calculated baseline eco-efficiency will be identified. Finally, the potential improvement of eco-efficiency will be assessed and scenarios will be formulated in order to identify barriers for technology uptake and measures to encourage technology implementation will be proposed. The progress of the project can be followed at the EcoWater project website [3]. The outputs from the development of the case studies will be cross-compared and used as a basis for the formulation of policy recommendations that could foster technology implementation and uptake in the relevant water use sectors.

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Economic efficiency and benefit to society:
Urban water systems are crucial for society. They are analysed in order to account for the different economic values and environmental impacts associated with water use by different actors and to assess opportunities and barriers for the uptake of innovations to improve the eco-efficiency of the whole system.

New insights on the environmental fate and effects of the "essential toxin" Selenium

Selenium is of key importance to human health due to its essential character as a trace element. Due to the mere trace concentrations present in the environment, its analysis is challenging and many aspects of selenium environmental chemistry are still little understood. This study tries to shed light on the environmental fate of selenium, linking its speciation to mobility, bioavailability and potential effects on model organisms.

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School of Life Sciences FHNW

Keywords: Selenium speciation, trace element cycling, selenium deficiency

Introduction

Selenium is a natural trace element that has been referred to as the "essential toxin", both being essential yet highly toxic to humans and animals. Human nutrition with selenium is a delicate balance, since levels that are considered sufficient (>40 µg / day) are only marginally lower than excess levels (>400 µg / day, recommendation by WHO). There are large geographical variations in selenium concentration, with selenium rich soils at times only separated by a few kilometres from selenium deficient soils. Causes for selenium contamination are usually assignable to anthropogenic activities (e.g. mining, combustion of fossil fuels or irrigation with naturally rich selenium rich waters) [1, 2] (Fig. 1). In contrast, factors that favour selenium deficiency are far less well understood. Whereas selenium contamination is usually a local or regional problem, selenium deficiency concerns more widespread areas, for instance large parts of China, Siberia, Japan and Korea. Overall, an estimated 0.5 to 1 billion people may be affected by selenium deficiency worldwide [3]. Most countries within Europe suffer from a risk of Se deficiency, most prominently Finland and parts of the UK, where soil selenium contents are particularly low. However, it should be stressed that selenium concentrations in forage usually fail to directly correspond to total selenium concentrations found in soil. This is due to the fact that so called *speciation*, i.e. the various chemical forms in which an element is present, determines the environmental fate of selenium to large extent. Depending on the species present selenium may be assimilated by plants, interact with the soil matrix leading to immobilization or even leach from soil. Therefore it is crucial to determine speciation when evaluating the selenium status of a soil. If one considers the mere trace concentrations in which selenium occurs in soils (usually well below 1 mg per kg), the inherent analytical challenge becomes evident, in particular regarding selenium deficient soils. Consequently, the study of selenium in natural environments requires highly sensitive and species-specific methods that are time- and cost-effective. In the frame of the present study, such a method based on online preconcentration Ion Chromatography Inductively Coupled Plasma Mass Spectrometry (IC-ICP-MS) was developed [4]. The applicability of the new method was proven on leachates of pristine volcanic ash collected from 7 different volcanos. Such ash-impacted soils are considered to be among the most fertile soils in the world, hosting 9% of the world's 1990 population living within 100 km of a historically active volcano [5].

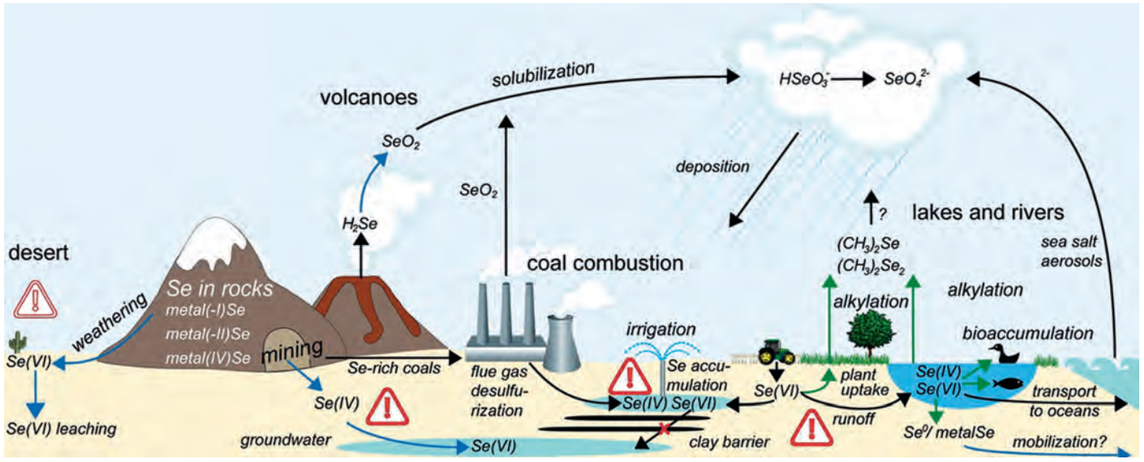

Figure 1 *Factors potentially leading to Se deficiency or excess (warning symbols). Reprinted with permission from Winkel et al.[2] © 2012 ACS.*

Results

A strong anion exchange column was online coupled to a Dionex 2100 IC system, equipped with an online eluent generator and self-regenerating suppressor, using a computer controlled automated switching valve. In this manner, samples of volumes between 40 µL and 8 mL can be preconcentrated, whereas the volume can be set using the chromatography software. Chromatographic separation of the analytes was achieved at 35°C using a flow of 0.5 mL min-1 and a multistep gradient of OH-. Peaks of the selenium species predominant in most aqueous environments – the oxyanions selenite

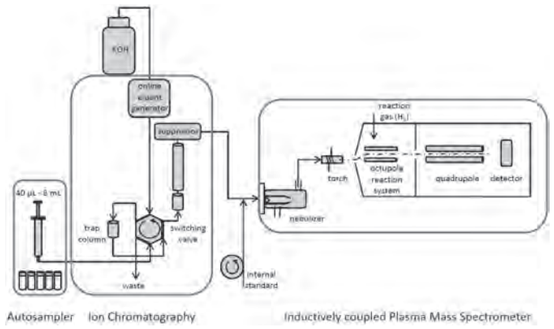

Figure 2 *Schematic of the analytical set up developed.*

(Se^{IV}) and selenate (Se^{VI}) - were separated within 300 seconds after injection and a total analytical time of 420 seconds was needed to equilibrate the analytical column for the subsequent injections.

Response for all three Se isotopes studied was linear to the total amount of Se^{IV} and Se^{VI} injected (i.e. volume×concentration), while the capacity of the preconcentration column was reached at more than 0.57 mg Cl^- (concentration×volume) injected. The instrumental set-up made use of two specific components that allowed the achieving of the required ultra-trace sensitivity: the electrolytic suppressor of the IC and the Octopole Reaction System (ORS) of the ICP-MS. Firstly, the suppressor was used to remove both cations and hydroxide anions from the mobile phase, which resulted in less interference and a stable eluent composition, beneficial for ICP-MS analysis. Secondly, the use of the ORS allowed monitoring of the selenium isotopes with the highest natural abundance (i.e. $^{78}Se^+$ with 23.5% and $^{80}Se^+$ 49.8%). These isotopes cannot be analysed by conventional ICP-MS, since they are prone to abundant Ar-Ar interference. Resulting Limits of Detection (LOD) and Limits of Quantification (LOQ) were in the low picogram range for all isotopes studied. The lowest LOD/LOQ were observed on ^{78}Se (2.3 and 7.3 pg total injected for selenite, 3.0 and 8.3 pg total injected for selenate, respectively).

The applicability of the method was then demonstrated on pristine volcanic ash of the volcanos Chaiten (Chile); Santiaguito (Guatemala); Fuego (Guatemala); Eyjafjalla jökull (Iceland); Etna (Italy); Sakura-jima (Japan); and Volcan de Colima (Mexico). For aqueous speciation samples were leached under shaking at a solid to water ratio 1:25 w/w following the standardized methodology for leachates of volcanic ashes. Only two samples contained a single Se species (selenite), while all other samples showed mixtures of different selenium species (oxyanions plus an additional unknown species). We could confirm for volcanic ashes that total Se content is not necessarily correlated to its mobility (assessed here by extent of selenium leached). For instance the Japanese sample showed little selenium leached (1%), while containing the highest (1.1 mg Se kg^{-1}) total Se concentration. Most other volcanic ashes studied were consistent in showing low leachability, since in only 2 out of 12 samples was more than 10% of the total Se found in the leachates.

Conclusion and Outlook

Due to the mere trace concentrations, environmental selenium speciation requires sophisticated, sensitive analytical techniques, commonly relying on a preconcentration step prior to ICP-MS analysis. Existing preconcentration methods are costly and labor intensive, yet more importantly time-consuming and often not species-specific, which may be a source of bias in redox sensitive selenium speciation. We described for the first time a novel, robust, work- and time-efficient analytical approach that overcomes all the latter disadvantages by automating the preconcentration step and coupling it online to IC-ICP-MS analysis. It does not require any sample preparation except filtration. With the method presented here it was possible to measure picogram amounts of the prevalent oxyanion (selenite, selenate) and further anionic species in an automated manner within 7 minutes. The volcanic ash leachates analysed showed a great variability in both selenium concentration and speciation, but were mostly characterized by low selenium leachability. The online coupling of IC-ICP-MS provides a tool for future routine analysis at ultra-traces, which are necessary to understand the environmental chemistry of selenium in volcanic ash impacted soils and in particular in selenium deficient areas. Furthermore, the method can be straightforwardly expanded to quantify other anions of environmental concern, such as arsenic, uranium, chromium and others.

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Research Focus Area:
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Partner
Lenny Winkel (EAWAG/ETH)
Funding
Swiss National Science Foundation (SNSF)

Economic efficiency and benefit to society

Selenium deficiency affects an estimated 0.5 to 1 billion people worldwide. Despite the considerable number of people affected, the mechanisms that lead to such deficiency are still little understood. The present study provides tools to analyse speciation in depleted environments, a prerequisite to more thoroughly understand and efficiently combat selenium deficiency by for instance improved fertilization.

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ATPS-Extraktion mit mikroporösen Membranen. Poster. ProcessNet Fachtagung Extraktion, Clausthal-Zellerfeld, 18.-20.04.2012

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Calixarenes and resorcinarenes: Macrocycles with (almost) unlimited possibilities for the design of self-assembling amphiphiles. Talk. 85th ACS Colloids and Surfaces Symposium, Montreal; 19.-22.06.2011

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Membrangestützte Flüssig-Flüssig Extraktion von fermentativ hergestellten molekularen Verbindungen mittels wässeriger Zwei-Phasen-Systeme. Talk. GVC/DECHEMA Vortrags- und Diskussionstagung Bioverfahrenstechnik an Grenzflächen, Potsdam, 30.5.-01.06.2011

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Reduction of excess alcohol during transesterification of various native oil sources. Poster. 8th ECCE together with ProcessNet-Annual Meeting and 1st ECAB together with 29th DECHEMA Biotechnology Annual Meeting, Berlin, 25.-29.09.2011

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Status of Water Reuse and Regulation in EU(REAU) member states. Talk. 8th IWA International Conference on Water Reuse, Barcelona, 26.-28.09.2011

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Kropf Ch, Zaja R, Segner H, Fent K.
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Institute for Medical and Analytical Technologies (IMA)

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Haefeli M, Schumacher R, Kalbermatten D, Schaefer DJ.
Rapid Prototyping and Manufacturing – innovative Applications in Hand Surgery. Talk. RapidTech 2012, Erfurt, 08.-09.05.2012

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Antimicrobial Effects Of Titanium Surfaces With Incorporated Copper. Poster. SSBE Annual Meeting, Bern, 22.-23.08.2011

Schkommodau E, Coigny F, Findeisen C, Hirschmann M, Ballweg C, Jürgens P, Thoranghatte R, Knobel B.
Handheld Surgical navigation System. Talk. World MedTec Forum, Lucerne, 25.09.2012.

Schkommodau E, Fabbri S, Jeker M, Schulze J, Bhavsar S, Graefe R, Baykut D, Egger Ch, Pittini R.
Feasibility of a Hollow-Rotor-Axial-Flow-Pump as ventricular assist device. Talk. Stepping Stone Symposium, Zürich, 28.09.2012

Schkommodau E.
Recent developments in the medical instruments field. Talk. Implant 2012 Conference, Lyon, 01.06.2012

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Feasibility of a Hollow Rotor Axial Flow Pump (Hotor) as VAD. Talk. International Society for Rotational Blood Pumps, Istanbul, 27.06.2012

Schkommodau E, Coigny F, Findeisen Ch, Hirschmann M, Ballweg Ch, Jürgens, Thoranghatte R, Knobel B.
Miniaturized navigation system for computer aided surgery. Talk. CAOS conference, Paris, 17.06.2011

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Beeinflussung des elastischen Verhaltens von künstlich hergestellten Knochenersatzstrukturen. Talk. MEET THE EXPERT, Interlaken, 11.-12.04.2011

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Charakterisierung von SLM gefertigten Knochenersatzstrukturen aus Titan. Talk. MEET THE EXPERT, Interlaken, 11.-12.04.2011

Schumacher R, Coigny F, Müller T, Näf M, Schkommodau E.
Specific design of bone grafts according to Hounsfield units. Talk. 45. Jahrestagung DGBMT, Freiburg, 27.-30.09.2011

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Laser Melting of cp Ti scaffolds: opportunities and limitations. Talk. Orthotec Europe, Zürich, 28.-29.09.2011

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Shah A, Coste J, Gmünder D, Ulla M, Lemaire JJ, Schkommodau E, Hemm S.
Quantitative rigidity and tremor evaluation using accelerometer during deep brain stimulation surgery - a preliminary study. Talk. XXth Congress of the European Society for stereotactic and functional neurosurgery. Lisbon 26.-29.09.2012

Shah A, Hemm S.
Acceleration measurements during DBS surgery for tremor. Talk. 1st international symposium on deep brain connectomics, Clermont-Ferrand, 28.-29.09.2012

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Quantitative tremor evaluation during deep brain stimulation surgery - a preliminary study. Talk. Annual Meeting of the Swiss Society of Biomedical Engineering, Lausanne, 27.-28.08.2012

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SASCIA: SmArt System for Cell Impedance Analysis. Poster. Biotech 2011, Wädenswil, 01.-02.09.2011

Stanimirov M, Sandoval L, Valdés J, Tabara D.
Miniaturized electrical impedance spectroscopy for intelligent implants. Talk. 20th Biovalley; Meet & Match Meeting: Intelligent implants, Strasburg, 20.05.2011

Stanimirov M, Lempen M, Koch V, Albrecht H, Kübler E, Valdés J, Tabara D, Sandoval L.
Miniaturized electrical impedance spectroscopy for intelligent sensors: The impedance pill. Poster. Biotech 2011, Wädenswil, 01.-02.09.2011

Stanimirov M, Lempen M, Koch V, Sandoval L.
Miniaturized electrical impedance spectroscopy for intelligent sensors. Talk. 21th Biovalley Meet & Match Meeting: Microfuidic, Karlsruhe, 28.09.2011

Wardell K, Richter J, Zsigmond P, Hemm S.
Optical measurements for Guidance during Deep Brain Stimulation Implantation. Talk. World congress in medical physics and biomedical engineering, Bejing, 26.-31.05.2012

Institute for Pharma Technology (IPT)

Ardjomand-Woelkart K, Kollroser M, Derendorf H, Bauer R, Butterweck V.
Herb-drug interactions: Effects of Echinacea preparations on Cytochrome P450 activities in rats. ICNPR Meeting, New York City, 28.07-01.08.2012

Butterweck, V.
What is the best strategy for preclinical testing of botanicals? 8th Brazilian Symposium of Pharmacognosy and 11th International Symposium of the Brazilian Society of Pharmacognosy, Ilheus, 18.-20.04.2012

De Kruif JK, Bravo R, Kuentz M.
Surface properties and flocculation fractal concept in pharmaceutical suspensions' Quality-by-Design. 9th Central European Symposium on Pharmaceutical Technology, Dubrovnik, 2.-22.09.2012

De Kruif JK, Bravo R, Kuentz, M.
Quality by Design of concentrated pharmaceutical suspensions - consideration of drug surface energy profiles and fractal particle flocculation. AAPS annual meeting and congress, Chicago, 25.-29.10.2012

Jarri S, Bravo R, Kuentz M.
Compatibility study of liquid-filled hard capsules with lipid formulations containing critical levels of co-solvents. AAPS annual meeting and congress, Chicago, 25.-29.10.2012

Joost, B.
Processing of Pharmaceutical Dispersions with Drug Substances of low Solubility, NanoFormulation2012, Barcelona, 28.05. – 1.06.2012

Joost, B.; Studer M.
Production of Drug loaded Liposomes with a novel Stirred Bead Mill, ACHEMA 2012, Frankfurt a.M., 18. – 22.06.2012

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Sedative Effects of Passiflora Edulis F. Favicarpa ans Passiflora Alata Extracts in Mica measured by Telemetry. ICNPR Meeting, New York City, 28.07-01.08.2012

Li L, Han A, Kinghorn AD, Frye R, Derendorf H, Butterweck V.
The Pharmacokinetic Properties of Pure ε-Mangostin in rats in Comparison to Mangosteen Extract. ICNPR Meeting, New York City, 28.07-01.08.2012

Misic Z, Muffler K, Sydow G, Kuentz M.
Starch-based PVA thermoplastic capsules for encapsulation of hydrophilic. SMEDDS Annual Research Meeting, Basel, 14.02.2012

Misic Z, Muffler K, Sydow G, Kuentz M.
Novel thermoplastic capsules for robust encapsulation of hydrophilic lipid-based formulations. 5th Swiss Pharma Science Day, Bern, 29.08.2012

Misic Z, Muffler K, Sydow G, Kuentz M.
Novel thermoplastic capsules for robust encapsulation of hydrophilic SMEDDS. 8th World Meeting on Pharmaceutics and Pharmaceutical Technology, Istanbul, 19.-22.03.2012

Misic Z, Muffler K, Sydow G, Kuentz M.
Biorelevant drug release studies of novel thermoplastic soft capsules. AAPS annual meeting and congress, Chicago, 25.-29.10.2012

Niederquell A, Kuentz M.
Diffusing wave spectroscopy for contact-free rheological analysis of self-emulsifying drug delivery systems. EuPAT 5, Ghent, 09.-10.05.2012.

Reufer M, Niederquell A, Völker AC, Kuentz M.
Micro-rheological characterization of emulsions. Swiss Soft Days, Lausanne, October, 2012.

Stillhart C, Imanidis G, Kuentz M.
Real-time monitoring of drug precipitation during in vitro lipolysis of lipid-based drug delivery systems. Globalization of Pharmaceutics Education Network GPEN Meeting, Melbourne, 27.-30.11.2012

Stillhart C, Kuentz M.
Is Raman spectroscopy a potential PAT tool for drug quantification in self-emulsifying drug delivery systems? 5th Swiss Pharma Science Day, Bern, 29.08.2012

Stillhart C, Kuentz M.
Is ultrasonic resonator technology an alternative to Raman spectroscopy for drug quantification in complex lipid-based formulations? EuPAT 5, Ghent, 09.-10.05.2012

Stillhart C, Kuentz M.
Raman spectroscopy as novel process analytical tool for drug quantification in self-emulsifying drug delivery systems. 8th World Meeting on Pharmaceutics and Pharmaceutical Technology, Istanbul, 19.-22.03.2012

Thormann U, Imanidis G.
Vehicle elicited improvement of intestinal absorption of a phytopharmaceutical compound in the Caco-2 model via increased stability and reduced metabolism. Globalization of Pharmaceutics Education Network GPEN Meeting, Melbourne, 27.-30.11.2012

U. Thormann, S. Verjee, G. Imanidis
Determination of degradation and saturation solubility of an unstable phytopharmaceutical compound-Swiss Pharma Science Day, Bern, Switzerland 29.8.2012

Research Portfolio

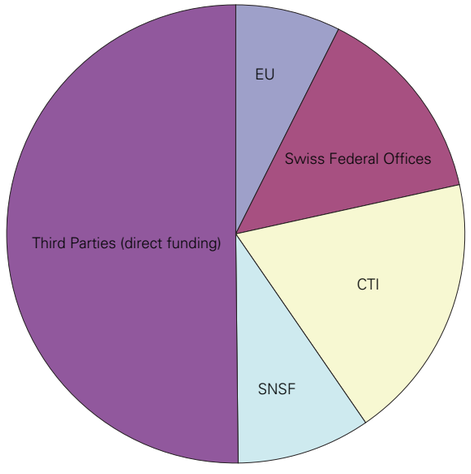
The School of Life Sciences FHNW has established itself as a competent address for qualified research. The cooperation with industrial and academic partners is strong and nowadays the School is part of many nationally and internationally funded projects. It is also active in promotion of spin-off companies. Within the last 2 years four new companies started.

The following tabe gives an overview:

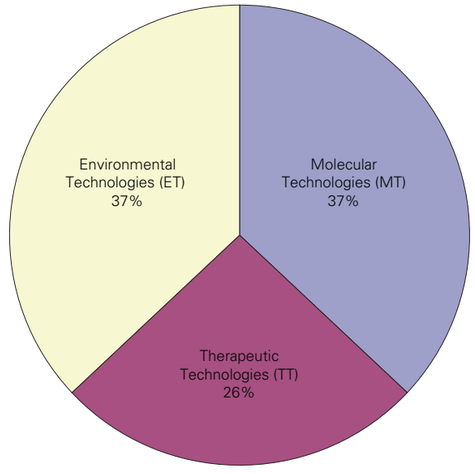
	10'000 – 100'000 CHF	> 100'000 CHF
Research Projects (2011-2012)	158	139

Spin-Off	Business Area
INOFEA GmbH	Design, development and production of innovative nanomaterials with remarkable recognition properties for industrial applications and products.
AlloCyte Pharmaceuticals AG	Drug discovery programs on therapeutically validated targets and translational clinic research to indications of high medical need.
MiniNaviDent AG	Innovative solutions in the area of dental implantology.
NeoMedz Sàrl	Designing and manufacturing of new tools and technologies for minimally invasive medical procedures.

Type of Funding (% of current projects)



Research Focus Areas (2011 – 2012)
(% of external Funds)



Research Fields and Competences

Institute	Fields of Research	Competences	Research Focus Area
Institute for Chemistry and Bioanalytics (ICB)	Biochemistry, Bioanalytics, Diagnostics (Bio)-Nanotechnology, Instrumental Analysis Organic Synthesis, Chemical Engineering	Biochemistry, Bioanalytics, Diagnostic (Bio)-Nanotechnology Molecular Recognition, Organo- and Biocatalysis Synthesis / Sustainable Development Molecular Diagnostics and Preclinical Development of Pharmaceuticals Instrumental Analytics Organic and Organometallic Synthesis Chemical Engineering	MT, TT
Institute for Ecopreneurship (IEC)	Resource Management, Cleaner Production Ecotoxicology Environmental, Biotechnology and Engineering	Environmental Engineering/Clean Technologies Ecotoxicology Environmental Biotechnology/Microbiology Ressource Management Cleaner Production in Industry (CP) Green Chemistry	MT, ET
Institute for Medical and Analytical Technologies (IMA)	Implant Development Biomedical Information Systems Surgical Systems and Methods	Medical Image Processing Visual Analytics Computer-assisted Surgery Medical Additive Manufacturing Deep Brain Stimulation Biosignal Processing Materials Science Microsystem Technology	TT
Institute for Pharma Technology (IPT)	Dosage Forms Drug Delivery Procedures and Production Processes	Formulation research and dosage form design and preparation Process development and process engineering Quality by design and process analytical technologies Intestinal and (trans)dermal drug delivery and absorption Pharmacokinetics and pharmacodynamics of natural products	MT, TT

Research Seminars
Autumn 2011–Summer 2013

Michael Stumm, F. Hoffmann-La Roche AG, Basel
Histopathology and Clinical Development: a Phase II Case Study

Jürg Noser, Kantonales Laboratorium, Basel
Spurenanalytik in der Lebensmitteluntersuchung

Joachim Köser, School of Life Sciences FHNW, Muttenz
Fluoride particles for oral care

Fatos Hoxha, School of Life Sciences FHNW, Muttenz
Design and study of catalysts for selective hydrogenations - an overview of ETH and future HLS projects

Jens Gobrecht, Paul Scherrer Institut PSI, Villigen
Micro- und Nanofabrikationstechnologien für Life Sciences und andere Anwendungen

Therese Bormann, School of Life Sciences FHNW, Muttenz
Memorymetalle / NiTi in der Medizinaltechnik

Atanas Koulov, Novartis Pharma AG, Basel
Protein Aggregation in Biopharmaceuticals - Why do we need to measure it and how

Gerhard Grundler, School of Life Sciences FHNW, Muttenz
Zucker ist nicht nur süss–Einblicke in die Kohlenhydratchemie

Giampiero Beroggi, Statistisches Amt Zürich, Zürich
Organizational Decision Making in Crisis Management

Roger Norcross, F. Hoffmann-La Roche AG, Basel
Medicinal Chemistry Optimisation and Selection of a Clinical Candidate for Psychiatric Diseases

Kaspar Fischer, Basel Institute on Governance, Basel
Information Security

Geo Adam, F. Hoffmann-La Roche AG, Basel
Neuropeptid Orphanin

Christoph Stamm, Zurich University of Applied Sciences, Zurich
Optische Biosensoren

Rong Ji, Nanjing University, Nanjing
Stimulated bioremediation of soil by earthworms

Eric Kübler, School of Life Sciences FHNW, Muttenz
Molekulare Diagnostik

Yannick Zimmermann, School of Life Sciences FHNW, Muttenz
SUNFLOWER project: Potential fate and effects of organic photovoltaics in the environment

Gerhard Trube, F. Hoffmann-La Roche AG, Basel
Neuronale GABAA-Rezeptoren in der präklinischen Forschung

Dirk Haubert, Novartis AG, Basel
Drug Discovery in Autoimmunity

Serge Reichlin, Siemens Schweiz AG, Zürich
Aktuelle Trends im Schweizer Gesundheitswesen mit Fokus auf Spitalfinanzierung

Ron Tynes, School of Life Sciences FHNW, Muttenz
The "Gene-to-Protein" Recombinant Protein Production Platform

Martin Graf, F. Hoffmann-La Roche AG, Basel
Stem Cells as Research Tool

Bernd Folkmer, HSG-IMIT, Villingen-Schwenningen
Energy Harvesting in der Medizintechnik und Umwelttechnologie

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