Master thesis 2021 -

Department of Pharmacy
Preface

This thesis catalogue is intended to provide inspiration and help you to get the thesis that suits you. The catalogue is structured in such a way that each research group, along with its supervisors, is described with examples of projects or project areas.

As you will not be writing your thesis until next year, these descriptions should be viewed as tentative only, the reason being that future research results may alter the projects. Therefore, the final projects will be defined by agreement with the students immediately before the projects are to start.

What might not be written in the catalogue is that most, if not all, supervisors apart from offering projects that are performed in the University facilities, also offer project in collaboration with other institutions/industry in Denmark or abroad. So if you find an interesting project area just ask for options as to where such a project can take place. To ensure a good experience there might be expectations to prior knowledge or grades depending on project placement, but do remember that grades are not everything and a good attitude will get you just as far as good grades.

So what do you do now? Look at the catalogue, see if some project or some supervisors sound interesting, and send an e-mail with the suggestion to meet.

Good advice when contacting your potential thesis supervisor:

1. Study the research conducted in your potential supervisor’s lab before you ask for a meeting
2. Don’t send out generic emails – tailor your emails for each potential supervisor you contact
3. Tell your potential future supervisor why you find their specific area of research interesting
4. Tell something about yourself in the email – your academic background and your interests
5. Remember to be ready to answer questions about details about your study program, the timing of your thesis work, how many ECTS points, and remember to ask if the supervisor recommends any elective courses

Good luck and hope to see many of you at the Department of Pharmacy.
IF teaching committee
Preface

Content

1. CNS Drug Delivery and Barrier Modelling
2. Copenhagen Centre for Regulatory Science
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4. LEO Foundation Center for Cutaneous Drug Delivery
5. Manufacturing and Materials
6. Microscale Analytical Systems
7. Pharmaceutical Physical and Analytical Chemistry
8. Protein Analysis
9. Physiological Pharmaceutics
10. Social and Clinical Pharmacy
11. Solid State Pharmaceutics
12. Surface and Colloid Chemistry
13. Toxicology and Drug Metabolism
14. Vaccine Design and Delivery
We investigate how we can overcome the barrier tissues in the body and deliver drug compounds at the site of action. The major focus is on transport of compounds through the blood-brain barrier, but we also have projects on intestinal absorption and efflux of drug compounds.

The practical work includes design of novel peptide drug compounds, physicochemical studies of drug compounds, prodrugs and model drug compounds, ADME studies in cell models and in vivo and characterization of relevant membrane transport proteins. Special focus is on peptides. A number of peptide drugs for the treatment of brain diseases are available. However, to reach their target site of action, they must pass the blood-brain barrier (BBB). The capillary endothelium comprises the major physical barrier of the BBB and allows only passive permeation of molecules <400 Da. Brain delivery of the larger biopharmaceuticals, which today includes an increasing number of novel peptide-drug entities, is therefore restricted; both due to their large molecular size and hydrophilic nature. Thus, the development of peptide-drugs for the treatment of brain specific diseases requires a delivery strategy for overcoming the endothelial BBB in order to reach its final target within the brain.

The group consists of one professor, two assistant professors, one research scientist, as well as technicians, PhD-students and Masters students. We work in a cross-disciplinary fashion, have a large international network and an exciting work environment.

Supervisors
Mie Kristensen  Assistant Professor  Mie.kristensen@sund.ku.dk  Tel. 35336063
Lasse Saaby  Research Scientist  lasse.saaby@sund.ku.dk  Tel. 35336325
Birger Brodin  Professor  birger.brodin@sund.ku.dk  Tel. 35336169
Project examples

Cell models for screening of CNS drug compounds

Industrial screening of CNS drug compound candidates involve the use of cell culture models. The project concerns characterization of drug transport in cell culture models developed by the group and investigation of their use in predicting blood-brain barrier permeability. The overall aim of the project is to generate predictive tools for CNS drug development.

Supervisors: Lasse Saaby & Birger Brodin
Max no of students: 3

Stability of cell-penetrating peptide conjugated therapeutic peptides in biological matrices and their adsorption to plasma proteins

The cell-penetrating peptides (CPPs) comprise a promising tool to facilitate delivery of macromolecular drug entities not only into cells but also across biological barriers, such as the BBB. However, due to their peptide nature they are prone to enzymatic degradation. In addition, cationic CPPs have been demonstrated to adsorb to plasma proteins, thus potentially hindering their cellular uptake.

With the present project, the CPP stability in relevant matrices (physiological buffer, cell culture media, plasma) as well as during incubation with brain endothelial cells (e.g. bEND3 cell line and a primary blood-brain barrier model) will be evaluated using e.g. HPLC, LC-MS, SDS-PAGE, and thin layer chromatography. In addition, CPP interaction with plasma proteins and its effect on uptake into brain endothelial cells will be evaluated via e.g. cell uptake studies and confocal microscopy.

Supervisor: Mie Kristensen
Max no of students: 3
Glycocalyx characterization on *in vitro* blood-brain barrier models

The cell-penetrating peptides (CPPs) comprise a promising tool to facilitate delivery of macromolecular drug entities not only into cells but also across biological barriers, such as the BBB. The mechanism by which CPPs translocate across cell membranes is widely discussed and both direct membrane translocation and endocytic uptake has been demonstrated. In addition, a number of studies suggest importance of CPP interactions with cell surface glycosaminoglycans (GAGs) prior endocytic uptake. GAGs are polysaccharide chains attached to a core protein unit making up the proteoglycans within the cell surface glycocalyx.

In order to obtain detailed knowledge on the potential involvement of GAGs for CPP membrane translocation, the glycocalyx layer on the cell culture model used for mechanistic studies must be well characterized. Furthermore, some studies question the presence of glycocalyx in endothelial cell culture.

With the present study we will characterize the glycocalyx surface lining primary mouse brain endothelial cells cultured as monoculture on permeable filters or in co-culture with mouse astrocytes. Employing antibodies and lectins we will identify the GAG composition and protein anchors as well as sugar moieties using confocal microscopy and Eastern blotting. In addition, electron microscopy may be applied to visualize the Glycocalyx morphology.

**Supervisor: Mie Kristensen**

**Max no of students: 3**
List of potential thesis supervisors:

Marieke De Bruin  
Professor, CORS director  
cors@sund.ku.dk

Christine E. Hallgreen  
Associate professor  
cors@sund.ku.dk

Short description of research field:

Medical research is a highly multidisciplinary field, which is impacted by scientific advances, new technologies, personalised medicine, and an improved understanding of patient requirements. However, the pharmaceutical development of innovative therapeutic solutions will not advance at a pace consonant with its promise without a simultaneous advance in the development of a flexible regulatory framework. This framework must be agile in meeting the competing goals of fostering innovation and protecting the public health, while integrating approaches to manage scientific uncertainty—the tools and trademark of regulatory science. With our research, we want to improve the drug regulatory system, by systematically studying its structure and behaviour as well as designing new tools to facilitate regulatory decision-making. Through improvement of the drug regulatory system, we aim to contribute to an improvement of the health of the society. Furthermore, we carry out research that produces evidence to be used in drug regulatory decision-making.
Marie Louise (Marieke) De Bruin
Professor, CORS director

Research focus: Marie Louise (Marieke) De Bruin was trained as a pharmacist and epidemiologist and has combined academic research with working for the regulatory authorities. She is an affiliate at the Utrecht University, WHO collaborating centre for pharmaceutical policy and regulation in the Netherlands. Furthermore, she was appointed by the European Commission as an independent scientific expert of the Pharmacovigilance Risk Assessment Committee (PRAC 2012-2018), that meets monthly at the European Medicines Agency in London; she is on the steering group of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP 2017-2019); and she is associate editor of the journal ‘Pharmacoepidemiology & Drug Safety’. Her research focusses on developing new tools, standards and approaches to evaluate the efficacy, safety, quality and performance of medical products in order to assess benefit-risk and facilitate a sound and transparent regulatory decision making.

Christine E Hallgreen
Associate professor

Research focus: Christine Erikstrup Hallgreen is an associate professor at the Copenhagen Centre for Regulatory Science. She has a background in engineering physics, and a PhD from Department of Physics at the Technical University of Denmark. In her professional career, she has been previously employed in the pharmaceutical industry (Novo Nordisk) and academia (Imperial College London). Christine has also conducted research at the National Institute of Health, Maryland, USA. In her research, she utilizes her quantitative and methodological training in the development and evaluation of drug regulatory tools and systems. Her research is motivated by a desire to describe and understand the functioning of the regulatory system and thereby optimize and improve the systems and regulatory tools set in place to promote public health. Her research includes development and evaluation of formal qualitative and quantitative methods to assess benefit-risk of pharmaceutical products, probabilistic methods to assess the effect of uncertainty in outcome data, and methods to collect preference values to support benefit-risk decisions.
Examples of projects

<table>
<thead>
<tr>
<th>Title</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>How best to protect public health: a comparative analysis of regulatory safety warnings on medicines in Australia, Canada, the European Union and the United States.</strong></td>
<td>Medicines have important health benefits but can also lead to harm. When new safety concerns arise, national regulatory agencies issue warnings to health professionals and the public. These warnings differ between countries, but no research has compared the effectiveness of different approaches. This study compares safety advisories on medicines in Australia, Canada, the United States, and the European Union in order to identify how to best protect public health. Within the project several working groups will focus on different aspects: discordancess in safety communication, regulatory policy analysis, qualitative analyses on HCP and patient perspectives, media analyses and pharmacoepidemiology to estimate health effects.</td>
</tr>
<tr>
<td><strong>Factors ensuring effective Direct to Healthcare Professional Communication of Risk Mininization</strong></td>
<td>Every day general practioners receive all kinds of new information about new medicines and new research. But what do they need in their everyday practice in front of their patients? How can we secure that they receive vital information about newly discovered medicine risk? Normally physicians and HCPs receive this kind of information in a letter. But that mode of communication is not very beneficial to physicians nor patients. For those reasons this project sets out to understand how general practitioners prefer receiving this information and what is important for them to know about medicine. With this knowledge future communications may better support the decisions they make when prescribing medicine.</td>
</tr>
<tr>
<td><strong>Similar but not identical: the changing regulatory landscape of biosimilars from the regulator, industry, professional, and patient perspectives</strong></td>
<td>A biosimilar is a biological medicine highly similar to another already approved biological medicine (the ‘reference medicine’) as defined by e.g. the European Medicines Agency (EMA). The European Union allowed the development of biosimilars in 2001, and since then biosimilar regulation has been introduced in the US and other countries. Introducing biosimilars aimed to foster competition and decrease health care costs. It can be expected that the various stakeholders (regulators, industry, prescribers, and patients) each have their view of what is similar enough and that such views may even differ significantly within those stakeholder groups. Unfortunately, little is known about how these different stakeholders interpret ‘high similarity’, and how these views influence the approval, development, and use of biosimilars.</td>
</tr>
<tr>
<td><strong>The Impact of Paediatric Regulations on Drug Development in a Trans-Atlantic Perspective</strong></td>
<td>The objective of this PhD project is to provide insights into the effectiveness of the EU and US paediatric regulations to promote access to medicines for children as well identifying potential barriers of the paediatric regulations to innovative drug development in general. Ultimately, these analyses should serve to provide recommendations for improvements to the global regulatory frameworks for paediatric medicines development with a focus on the US and the EU.</td>
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</tbody>
</table>

**Note:** If you are interested in writing your thesis with CORS, please visit us the MSc thesis orientation day on October 25, 2019. Hence, we ask student to write a short motivation (250 words) to cors@sund.ku.dk (deadline November 6, 2019). Selected students will be invited for a meeting at our open house on November 11, 2019 (13.00-1.00) to discuss further.
3 Drug Delivery and Biophysics of Biopharmaceuticals

https://pharmacy.ku.dk/research/drug-delivery-biophysics-biopharmaceuticals/

**Short description of research field:** Our research focus is the design and development of optimal drug formulations with a focus on biopharmaceuticals, specifically peptides and proteins, used for e.g. metabolic diseases or infections. Our research spans from physico-chemical analysis of stability, and biomembrane interactions via design of advanced drug delivery systems, to assessment of the efficacy in cell culture models and animals. We aim to gain detailed, fundamental, and mechanistic understanding of the challenges associated with these molecules when administered via injectable and non-injectable routes.

**List of potential thesis supervisors:**

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  Hanne.morck@sund.ku.dk

- **Urs Häfeli**
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- **Marco van de Weert**
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  13, 3, room number 335
  Marco.vandeweert@sund.ku.dk

- **Vito Foderà**
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  Building 13, floor 3, room number 332
  Vito.fodera@sund.ku.dk

- **Feng Wan**
  Assistant Professor
  13, 3, room number 317
  Feng.wan@sund.ku.dk

- **Jijo Vallooran Joy**
  Assistant Professor
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  jijo.vallooran@sund.ku.dk

- **Stine Harloff-Helleberg**
  Assistant Professor
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**Examples of projects are shown on the following pages. Contact us for more details on our projects and possibilities.**
**Hanne Mørck Nielsen**  
Professor, PhD  
13, 3, 337 Email: [hanne.morck@sund.ku.dk](mailto:hanne.morck@sund.ku.dk)

### Research focus:
Drug delivery of peptides and proteins (biopharmaceuticals) and antimicrobial drugs. Oral peptide delivery, drug delivery systems, nanogels, cell-penetrating peptides, biomembrane interactions, mucus, cell uptake and transport processes

### Oral permeation enhancers interactions and influence on the intestinal mucus barrier
An approach to enhance uptake of biopharmaceuticals across oral mucosa is to co-formulate the drug with a permeation enhancer (PE). Mechanisms of actions of PEs including mucus effects are generally poorly understood. We aim is to investigate and assess if possible interaction alters the PE’s properties or alters mucus barrier properties using *in vitro* and *ex vivo* models.

**Supervisor:** PhD student Janni Støvring Mortensen, Stine Harloff-Helleberg and Hanne Mørck Nielsen

### Cell-penetrating peptides and other excipient use in drug delivery
Understanding of interactions between drugs, excipients and biological membranes are of crucial importance to improve the current drug delivery systems with peptide drugs. We focus on functional excipients that interact with cell membranes. Cell culture models as well as biophysical techniques are applied to investigate different enhancer and active molecules.

**Supervisor:** PhD student Ragna Guldsmed Diedrichsen and Hanne Mørck Nielsen

### Intercellular junctions’ role in drug delivery
When studying drug delivery across epithelial barriers, e.g. the intestinal barrier, one of the key properties is the tightness of the epithelium due to the presence of junctions between the cells. This tightness is crucial for the normal function of the tissue, but may also be a target site for enhancing drug delivery. We investigate the junction dynamics, and the possibilities for targeted delivery via this route.

**Supervisor:** PhD student Danai Anastasia Panou and Hanne Mørck Nielsen

### Antimicrobial peptide (AMPs) and antibiotics formulation design
Combatting infections is a highly challenging task because antimicrobial drugs have difficulties in reaching the bacteria in e.g. biofilms in sufficient amounts. We formulate AMPs in for example novel polymeric nanogels, characterize and evaluate their effect in killing bacteria and removing bacterial biofilm.

**Supervisor:** Post doc Sylvia Klodzinska and Hanne Mørck Nielsen

### Biobarriers in oral drug delivery: investigating model cell membranes and interactions
This interdisciplinary project will cover the preparation of liposomes with different compositions, functionalization of microparticles with lipid bilayers as model membranes and with different drug excipients, and characterization of the interactions using optical tweezers. Optical tweezers help to characterize interactions and binding forces between biologically relevant molecules, with single-molecule sensitivity.

**Supervisor:** Post doc Ada-ioana Bunea (DTU) and Hanne Mørck Nielsen
### Examples of projects

#### Characterizing ligand binding to proteins

<table>
<thead>
<tr>
<th>The pharmacological effect of drugs usually depends on their binding to a target protein and to plasma proteins. Protein binding can also be used to stabilize therapeutic proteins. It is therefore important to characterize this so-called ligand binding to proteins using a set of analytical methods. To do this characterization properly can be a challenge, however.</th>
<th>In this project you will use several advanced analytical methods to characterize binding of model ligands to model proteins, and test different published approaches to analyze the data. You will thereby get a solid understanding of the advantages and limitations of various methods, and learn how to critically assess the literature on this topic.</th>
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<tr>
<td><strong>Supervisors:</strong> Marco van de Weert</td>
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#### Characterization of lipitated peptides (provisional)

<table>
<thead>
<tr>
<th>Lipidation can be used to extend the half-life of therapeutic peptides. Although proven successful in the clinic, it is a considerable challenge to characterize these lipitated peptides in terms of stability, self-association, and structure. In this project you will work with a small biotech company that produces these lipitated peptides. Depending on the project duration, you will...</th>
<th>...characterize one or more such lipitated peptides using advanced methods like light scattering, small-angle X-ray scattering, circular dichroism, or focus on the chemical instability of these peptides as determined by HPLC coupled to mass spectrometry. A part or the whole project may be executed at the company itself.</th>
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<td><strong>Supervisors:</strong> Marco van de Weert + company supervisor (provisional)</td>
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#### Physical instability of peptides

<table>
<thead>
<tr>
<th>Therapeutic peptides offer many advantages, but their instability is often a major formulation challenge. Many peptides tend to aggregate into long fibrillar structures. Preventing this fibrillation is a major challenge. Within this area you can go into some fundamental aspects of peptide (or protein!) fibrillation, and study how the fibrillation process is changed by using heavy water (D₂O).</th>
<th>A second, more practically oriented project is to study the impact of various excipients on the instability of some model compounds. This project may be performed at, or in collaboration with, a local company. In both projects you will use a panel of advanced analytical techniques to study the aggregation process.</th>
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<tbody>
<tr>
<td><strong>Supervisors:</strong> Marco van de Weert + Vito Foderà or company supervisor</td>
<td></td>
</tr>
</tbody>
</table>
### Vito Foderà

**Associate Professor, PhD**  
13, 3, 332  
Email: vito.fodera@sund.ku.dk

### Research focus:
Protein science; neurodegenerative diseases; biomaterials for drug delivery;  
X-ray and neutron science, microscopy and optical and IR spectroscopy  
*If you want to look at my research focus, please visit:* [https://www.vitofodera.com/](https://www.vitofodera.com/)

### Examples of projects *NB: we can design the project that suits you best. Come and talk to us!*

<table>
<thead>
<tr>
<th>Role of Protein-Protein interactions in the formation of protein superstructures</th>
<th>![Image of fibrils, particulates, spherulites, and networks]</th>
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<tbody>
<tr>
<td>Protein-protein interactions are regulated by the physicochemical properties of the solution. Co-solvents (e.g. alcohols), pH and mechanical stress strongly affect such interactions having as a final result the modification of the aggregation reaction. With this project we want to investigate what is the effect of different parameters on both the kinetics of formation and the structure of superstructures.</td>
<td><strong>Supervisor:</strong> Vito Foderà and Marco van de Weert</td>
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</table>

<table>
<thead>
<tr>
<th>Amyloidogenic protein interaction with cell membranes</th>
<th>![Image of amyloid fibrils]</th>
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<tbody>
<tr>
<td>The formation of amyloid fibrils is considered to play a key role in the development of pathologies such as Parkinson’s and Alzheimer’s diseases. New view supports the concept that the interactions of amyloidogenic proteins with cell membranes are a key factor in regulating related toxicity mechanisms. Aim of this project is to directly observe the progression of amyloid fibril formation in the presence of membranes both in synthetic model systems and in living cells.</td>
<td><strong>Supervisor:</strong> Vito Foderà and Jijo Vallooran</td>
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<table>
<thead>
<tr>
<th>Protein-based biomaterials for drug delivery</th>
<th>![Image of protein aggregates]</th>
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<tbody>
<tr>
<td>A new frontier in protein self-assembly is represented by the analysis of the protein aggregate in terms of its mechanical/structural properties. This is pivotal for the use of protein aggregates as biomaterials for drug delivery. Aim of this project is to design and produce protein-based materials using different processing methodologies, from electrospinning techniques and bulk methods to microfluidic chips.</td>
<td><strong>Supervisor:</strong> Vito Foderà and Jijo Vallooran</td>
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<tr>
<th>Protein stability in pharmaceutical formulations</th>
<th>![Image of protein drug products]</th>
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<tbody>
<tr>
<td>The presence of protein aggregates in protein drug products is a major concern in pharmaceutical industry. These particles may alter the efficacy of the product. As a consequence, it is of great relevance to isolate and characterize each of these types of particles and evaluate their risk profile. Aim of this project is to produce and analyze homogeneous populations of protein aggregates originated from insulin formulations.</td>
<td><strong>Supervisor:</strong> Vito Foderà + company supervisor</td>
</tr>
</tbody>
</table>
**Jijo Vallooran**  
Assistant Professor  
13, 3, 315 Email: jijo.vallooran@sund.ku.dk

**Research focus:**  
Lipid and Protein Self-assembly; Nanostructured biomaterials for drug delivery; Nanostructured material characterization using Scattering Techniques.

<table>
<thead>
<tr>
<th><strong>Electric field assisted drug delivery from Protein biomaterials</strong></th>
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<tr>
<td>Stimuli-responsive or “smart” protein biomaterials are of great interest in the fields of biopharmaceuticals and medicine. Drug delivery systems based on stimulus responsive materials for controlled and long-term drug release under external electric field offer the promise of new treatments for chronic diseases that require daily injections or precise doses of medication. Aim of this project is to study the effect of electric field on protein-based materials and its suitability for drug-delivery.</td>
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<tr>
<td><strong>Supervisor:</strong> Jijo Vallooran and Vito Foderà</td>
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<table>
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<tr>
<th><strong>Improving biopharmaceutical stability using Lipids</strong></th>
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<tr>
<td>Formation of aggregates in biopharmaceutical formulation continues to be one of the major quality concerns in biotherapeutics development. The presence of large quantities of aggregates is believed to be one of the causes of unwanted immunogenic responses. Protein particulates can form in a wide range of sizes and shapes. Lipids can generally bind on proteins and peptides, which could lead to improved stability. Aim of this project is to inhibit the protein aggregation in presence of medium-chain fatty acids and lipids.</td>
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<tr>
<td><strong>Supervisor:</strong> Jijo Vallooran, Marco van de Weert and Vito Foderà</td>
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<tr>
<th><strong>Designing compact lipid nanostructures for oral drug-delivery</strong></th>
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<tr>
<td>Oral drug delivery is the most preferred and convenient route of drug administration due to high patient compliance, cost-effectiveness, and flexibility in the design of dosage form. Due to the excellent biocompatibility and ability to solubilize both hydrophilic and hydrophobic drugs, lipid nanostructures are prominent nano-carriers for oral drug-delivery. However, the effectiveness of these lipid nanostructures can be significantly reduced due to lipase enzymatic digestion in the stomach as well as pH dependent structural changes. Aim of this project is to design compact lipid nanostructures, which does not affect by intrinsic physiological factors.</td>
</tr>
<tr>
<td><strong>Supervisor:</strong> Jijo Vallooran, Vito Foderà and Hanne Mørck Nielsen</td>
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</tbody>
</table>
Chemo-photothermal therapy combination for synergistic anti-biofilm infection effect

In this master thesis, we intend to exploit a graphene quantum dots (GQDs)-mediated strategy to achieve the chemo-photothermal therapy combination for synergistic anti-biofilm infection effect. GQDs, as a new class of nanomaterials, have shown strong antibacterial activity via various mechanisms, including disrupting bacterial membranes and generating reactive oxygen species when photoexcited. We hypothesize that a synergistic anti-biofilm infection effect, even the complete eradication of biofilm, can be achieved by using graphene-based ‘nanoantibiotics’ which combines multiple novel therapeutic strategies with conventional antibiotic treatment to combat the resistant mechanisms of biofilms. To prove the concept, we aim at reconstituting a biomimetic nanoparticles composed of a GQDs-based core loading with multiple therapeutic agents (e.g. conventional antibiotics, antimicrobial peptides, and quorum sensor inhibitor) and a biomaterials (e.g. lipids)-based shell.

Supervisor: Feng Wan and Hanne Mørck Nielsen

Biomimetic nanoparticles for effective delivery of immunomodulators to resolve the chronic inflammation in COPD

Chronic obstructive pulmonary disease (COPD) is characterized by complex chronic inflammation of the peripheral airways and lung parenchyma with impaired innate defense, resulting in progressive loss of pulmonary function. Innate immune modulation using immunomodulatory drugs may bring new perspectives in resolving abnormal inflammation and restoring immune homeostasis. In this master project, we intend to design biomimetic nanoparticles that can cater to the complex pathological microenvironment (e.g. pH value, enzymes) in the lungs with COPD, overcome the diverse biological barriers (e.g. pulmonary surfactants, abnormally viscous mucus), and accomplish intracellular delivery and release of payloads into their targets in the innate immune cells in the lungs with COPD.

Supervisor: Feng Wan and Hanne Mørck Nielsen
## Drug Delivery, Nanomedicines and Radiopharmaceuticals

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Professor, PhD  
Building 13, 3rd floor, room 318  
Email: urs.hafeli@sund.ku.dk

*For a list of publications and details of our lab, see: [http://www.magneticmicrosphere.com/hafeli_lab/](http://www.magneticmicrosphere.com/hafeli_lab/)*

<table>
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<tr>
<th>Research Areas</th>
<th>Main Experimental Techniques</th>
<th>Toxicity Assays</th>
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</thead>
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<tr>
<td>Targeted Drug Delivery</td>
<td>Cell Culture and In Vivo Tests</td>
<td>SPECT/PET/CT Imaging</td>
</tr>
<tr>
<td>Nanomedicine Synthesis and Testing</td>
<td>Protein Assays, Gels</td>
<td></td>
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<tr>
<td>Nanoparticles, Microspheres, Liposomes</td>
<td>Scanning Electron Microscopy</td>
<td>CyTOF, FACS, Confocal</td>
</tr>
<tr>
<td>Antibodies, Aptamers, Peptides</td>
<td>Radiolabeling and Quality Control</td>
<td>Chemical Conjugations</td>
</tr>
</tbody>
</table>

### Examples of typical MSc projects:
As all projects require a few months of training in the techniques used, we will only take students for a full 12 months. All these MSc projects will take place in Vancouver, BC, Canada. We will gladly give you the names of previous MSc students, so that you can find out from them what to expect. *For more details, please contact us directly!*

### Biodistribution of a Therapeutic Antibody In Vivo
More and more therapeutic antibodies are being developed for the treatment of many different diseases. Common applications include cancer therapy, where they can elicit an effect by themselves, or through a cytotoxic drug or a radioactive isotope, delivered with high efficiency to the target tissue. We typically make the antibody of interest radioactive, measure its stability and cell binding *in vitro*, and then determine *in vivo* (mainly by SPECT/PET/CT imaging) its biodistribution and potential toxicity. You as the student will learn all techniques needed.

### Development of Less Toxic but More Effective Antibiotics
Many antibiotics are toxic at effective concentrations. We are interested in delivering the antibiotics as nanomedicines that don’t have side effects, for example encapsulated in nanoparticles and microspheres, or bound to polymers. This requires the formulation and optimization of the nanomedicines, their testing *in vitro* (in minimum inhibitory concentration determinations) as well as *in vivo* (abscess model). If found effective, biodistribution studies will follow. You as the student will learn all techniques needed.

### Testing of Novel Excipients to Allow for Oral Delivery of Biopharmaceuticals
Many biopharmaceuticals, such as insulin and therapeutic peptides would benefit from being able to be taken orally, as many patients fear injections. We are investigating new polymer- and lipid-based excipients that might allow for the oral delivery of drugs. To determine the fate of the drug and the excipient separately, we make them radioactive and/or fluorescent and then follow them at the same time *in vitro* and *in vivo*. The main technique to be used is diagnostic imaging by SPECT/PET/CT.
4 LEO Foundation Center for Cutaneous Drug Delivery

https://pharmacy.ku.dk/research/lfccdd/

List of potential thesis supervisors:

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Office</th>
<th>E-mail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martin Malmsten</td>
<td>Professor</td>
<td>13:305</td>
<td><a href="mailto:Martin.malmsten@sund.ku.dk">Martin.malmsten@sund.ku.dk</a></td>
</tr>
<tr>
<td>Andrea Heinz</td>
<td>Associate Professor</td>
<td>13:310</td>
<td><a href="mailto:Andrea.Heinz@sund.ku.dk">Andrea.Heinz@sund.ku.dk</a></td>
</tr>
<tr>
<td>Kathryn Browning</td>
<td>Assistant Professor</td>
<td>13:305A</td>
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</tr>
<tr>
<td>Mariena van der Plas</td>
<td>Associate Professor</td>
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<td><a href="mailto:Mariena.van_der_Plas@sund.ku.dk">Mariena.van_der_Plas@sund.ku.dk</a></td>
</tr>
</tbody>
</table>

Short description of research field:

The aim of the center is to contribute to an integrating knowledge on skin as a barrier for drug absorption, and key properties of drugs and excipients for cutaneous drug delivery. Based on a predominantly physicochemical approach, we aim to develop methods for the rational development of novel drug delivery systems for cutaneous and transcutaneous delivery of both small and large molecules, ranging from wounds to intact skin.
**Examples of projects**

<table>
<thead>
<tr>
<th><strong>Membrane interactions of gold nanoparticles as antimicrobial agents</strong></th>
<th>Furthermore, gold nanoparticles may be locally heated by light, which can be used for killing even multi-resistant and biofilm-forming pathogens. Within the project, factors determining membrane interactions of gold nanoparticles will therefore be investigated by previously developed model lipid membranes, in combination with various biophysical techniques, such as QCM-D, ATR-IR, and light scattering. Results from such biophysical studies, e.g., on effects of membrane composition, size and surface properties of the gold nanoparticles, and effects of co-administration of such particles with other potent antimicrobial agents, notably antimicrobial peptides, will be correlated to biological results on antimicrobial effects and cell toxicity for selected systems.</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the present project, membrane interactions will be investigated for gold nanoparticles, which offer opportunities in combating challenging infections. For example, both low molecular weight and biomacromolecular drugs can be readily adsorbed at the surface of these nanoparticles, allowing large drug loads due to their large specific surface area. In addition, metal nanoparticles (including gold) display potent antimicrobial effects by themselves. The latter originate from several mechanisms, including direct membrane rupture, binding to sulfhydryl groups of metabolic enzymes, binding to microbial DNA, and generation of reactive oxygen species, in turn causing bacterial enzyme and lipid oxidation.</td>
<td></td>
</tr>
<tr>
<td><strong>Supervisors:</strong> Martin Malmsten &amp; Elisa Parra-Ortiz</td>
<td><strong>Supervisors:</strong> Martin Malmsten &amp; Elisa Parra-Ortiz</td>
</tr>
</tbody>
</table>
Kathryn Browning  
Assistant Professor  
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**Research focus:** Neutron reflectivity, skin lipid organization, lipid membrane interactions with nanomaterials and antimicrobial peptides

<table>
<thead>
<tr>
<th>Examples of projects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro modelling of the skin barrier for cutaneous drug delivery</strong></td>
</tr>
<tr>
<td>The stratum corneum, the outermost layer of the skin, is the main barrier between the body and its external environment protecting against water loss, and incoming pathogens and/or allergens. It is formed of a complex mixture of dead cells (corneocytes) imbedded in a lipid matrix. Drugs applied topically must pass through this barrier to reach the target; therefore, modelling human skin allows us to predict and understand the ADME properties of topical drugs and design more efficient transport vehicles. Furthermore, skin diseases such as atopic dermatitis and psoriasis are known to affect the lipids present in the stratum corneum, making the barrier leakier and the patient more prone to infection. By understanding drug interactions with both healthy and diseased stratum corneum we can better design drugs and formulations to cross the stratum corneum.</td>
</tr>
<tr>
<td>In this project, you will be isolating stratum corneum from pig ears, and testing the barrier properties of whole stratum corneum and extracted stratum corneum lipids with and without corneocytes. In this line of research, we use physical chemistry and surface science methods to investigate the molecular structure and interactions between the stratum corneum, drugs and formulations. Techniques such as ATR-FTIR, SAXS and neutron reflection will be coupled with more traditional pharmaceutical transport experiments using Franz cells. Using these techniques, we are able to study skin interactions with a wide range of molecules of interest, for example, common topical drugs, dermal penetration enhancers, excipients, formulations, skin irritants and allergens. This project provides an excellent opportunity for you to take control of your studies and steer the project in the direction you find to be the most interesting. It may also be possible to be involved in a neutron reflection experiment at a large-scale neutron scattering facility in the UK or France.</td>
</tr>
</tbody>
</table>

**Supervisors:** Kathryn Browning
Examples of projects

### Development of peptide-based electrospun wound dressings

Wound healing is a major burden to healthcare systems worldwide, and there is a clinical need for dressings that can be used to treat partial thickness burn wounds that affect the epidermal and dermal layers of the skin. Requirements for ideal wound dressings include the ability to prevent infection and maintain skin hydration. The wound dressing should further be non-toxic, non-immunogenic and should enhance tissue regeneration. Peptide-based electrospun wound dressings fulfill these criteria. This project focuses on the development of an electrospinning method to produce peptide-based wound dressings.

**Supervisors:** Andrea Heinz

The peptide will either be electrospun in a mixture with a polymer or co-axially electrospun (peptide core surrounded by polymer mantle). The electrospun fibers will then be comprehensively characterized by a range of analytical techniques, including scanning electron microscopy, X-ray powder diffraction and differential scanning calorimetry. The release of the peptide from the fibers will also be determined.

### Development of peptide-based nano- and microgels for the treatment of Ichthyosis vulgaris

Ichthyosis vulgaris (IV) is a relatively common skin condition that causes dry skin and strongly increases the risk of atopic dermatitis (AD). Individuals with IV have a flaky and dry skin and increased occurrence of hair follicle plugging on the upper arms and shoulders. As the disorder is caused by a loss-of-function mutation in the filaggrin (FLG) gene, replacement of the protein FLG shows great potential for relieving symptoms of IV and significantly improving the quality of life of IV patients.

This project will develop nanogel formulations containing FLG peptides for the treatment of IV and AD. The nanogel formulations contain a novel class of polyethylene glycol-based excipients. Systematic investigation of the physicochemical properties of the nanogel formulations with and without peptides will allow optimizing the systems with respect to their (a) physical stability during storage and sterilization, (b) protein release, (c) biocompatibility and (d) pharmaceutical performance with respect to treatment of IV.

**Supervisors:** Andrea Heinz
### Examples of projects

#### Development of novel peptide-based antimicrobial dressings for wound healing
With the increasing occurrence of resistance in bacteria, development of alternatives to antibiotics are essential. The goal of this project is the development of antimicrobial and immunomodulatory peptide-based dressings using electrospinning. The work will comprise optimisation of peptide-incorporation in/on the electrospun fibres, analysis of peptide-release kinetics, *in vitro* antimicrobial assays and, if time allows, *in vitro* biofilm and immunological assays as well.

**Supervisors:** Mariena van der Plas & Andrea Heinz

#### Peptide-based drug delivery systems for atopic dermatitis skin infections
Atopic dermatitis (AD) is a multifactorial relapsing inflammatory skin disease affecting 1 out of 5 Danish children. As decreased levels of antimicrobial peptides are a popular explanation for the observed increased susceptibility to infection in these patients, antimicrobial and immunosuppressing peptides have great therapeutic potential in AD. The goal of this project is the development of potent and safe peptide delivery systems for treatment of AD lesions.

The work will comprise optimisation of drug formulation, *in vitro* antimicrobial and biofilm assays and, if time allows, *in vitro* immunological assays as well. As we have various peptides to be tested, this project can be performed independently by multiple students.

**Supervisors:** Mariena van der Plas & Martin Malmsten
**5 Manufacturing and Materials**

https://pharmacy.ku.dk/research/manufacturing-materials/

<table>
<thead>
<tr>
<th>List of potential thesis supervisors:</th>
</tr>
</thead>
<tbody>
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<tr>
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</tr>
</tbody>
</table>

**Short description of research field:**

The Manufacturing and Materials group is focusing on processing and material sciences around solid state and semisolid pharmaceuticals. This international group has over 20 PhD students, postdocs and assistant/associate professors. The section is aiming for understanding the chemical and physical properties of the active pharmaceutical ingredients, both small molecules and bio-macromolecules, and excipients in relation to their processing behaviour. Further, the group aims to optimize stability and bioavailability of the final dosage form. The research is focusing on facilitating the future implementation of Quality by Design (QbD) principles for drug development processes, as well as implementation of process analytical technologies (PAT) for industrially relevant applications.

We focus on processing of small-molecule and protein/peptide-based medicinal products. Our goal is to understand the properties of active pharmaceutical ingredients and excipients in relation to their processing behaviour, and further, in relation to the optimal bioavailability of the final dosage form.
Examples of projects

**Hot melt processing of biopharmaceuticals**

In this project, the amorphous environment created by various polymers in a hot melt process will be studied to see whether it is sufficient to prevent the degradation caused by heat, and therefore would enable protein formulations to be produced by hot melt processing. This will be investigated by monitoring structural changes in both the solid and the liquid state. Several process and formulation variables form a good basis for the application of Design of experiments (DoE).

**Supervisors:** Lene Jørgensen and Johan Peter Bøtker

**Physical stability of proteins**

Maintaining the physical stability of proteins is crucial in both formulation and manufacturing, since the biological activity may otherwise be reduced. We will expose a protein to various types of stresses, formulation components, processing and use advanced techniques to characterize the changes that we observed. In this project, you will gain knowledge of basic protein formulation, effect from various types processing and excipients and you will get experience with techniques to study protein stability and structure.

**Supervisors:** Lene Jørgensen

**Master project in industry or abroad**

You could also do your project in the pharmaceutical industry, Medico industry or at a University abroad (e.g. University of Otago, School of Pharmacy, Dunedin, New Zealand). This requires planning, so short notice project are often not possible. You need to plan 6 months-1 year ahead. You will be asked to supply a copy of your grades, as you will need to work independently. The projects topics in industry are typically defined in detail 2-3 months before the actual start of the project.

**Supervisors:** Lene Jørgensen
Examples of projects

**Information-rich pharmaceutical products**

Information-rich dosage forms, i.e., cryptopharmaceuticals enables encapsulation both the drug and the sensitive information in a single unit. This can pave the way against counterfeiting of medicine. The goal of the project is to explore the further possibilities of efficient and secure data storage within edible drug-containing dosage unit.

**Supervisors:** Natalja Genina and External from the Department of Computer Sciences

**Feasibility of printed medicine**

Currently, there is only one commercially available 3D printed medicine. If the needs of the patients are identified, the situation can be different in the near future with more printed drugs coming to the market to provide more exact pharmaceutical treatment in society. The aim of the project is to explore the patients’ attitude towards the idea of getting personalized digital drug product by conducting interviews and showing the possibilities of 3D printing.

**Supervisors:** Natalja Genina and Sofia K. Sporrong

**Development of personalized medicine by 2D and 3D printing**

Delivering an accurate dose of active pharmaceutical ingredients (API) and tailoring their release profile are the key factors to produce efficient pharmacotherapy. With current dosage forms, tunable dosing and tailoring multidrug products’ properties are difficult and perilous. The evident flexibility of the printing technology allows commercial on-demand fabrication of individualized dosage forms. The overall goal is to produce novel solid dosage forms with easily adjustable doses and release profiles.

**Supervisors:** Natalja Genina and Johan Bøtker
<table>
<thead>
<tr>
<th><strong>Examples of projects</strong></th>
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<tbody>
<tr>
<td><strong>Image analysis of pharmaceuticals</strong></td>
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In this project, image analysis of e.g. the tablet coating quality is investigated using MATLAB programming. The project will revolve around creating MATLAB scripts for segmenting objects in images and constructing and operating analytical scripts as well as artificial neural networks for classification purposes. This project will thus focus on optimizing both the process of obtaining the images and the programming needed to analyse the images.

**Supervisors:** Johan Peter Bøtker
<table>
<thead>
<tr>
<th>Examples of projects</th>
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<tbody>
<tr>
<td><strong>Optimization of bulk properties of pharmaceuticals</strong></td>
</tr>
<tr>
<td>Particle properties determine the successful manufacturing of solid dosage forms. Shape and size distributions are critical parameters affecting flow ability of materials. However, it is a huge scientific challenge to translate these particle characteristics into optimal final formulation. There are several new innovative approaches to investigate powder rheology together with solid form analysis, making a huge impact in commercial scale process and product optimization. This project will investigate powder rheology as a part of solid dosage form development, as well as implementation of process analytical technologies (PAT) in an industrial setting. The projects topics in industry are typically finalized in detail 2-3 months before the actual start of the project. This project can also be performed as an industrial project at AstraZeneca, LEO Pharma, Lundbeck or Novo Nordisk.</td>
</tr>
</tbody>
</table>

**Supervisors:**
- **Internal supervisors:** Jukka Rantanen
- **External supervisors:** AstraZeneca, LEO Pharma, Lundbeck or Novo Nordisk
Examples of projects

**Pulmonary drug delivery**

Lung diseases including chronic obstructive pulmonary disease (COPD), respiratory infections and lung cancer are leading cause of death world-wide. Inhaled drugs can directly reach the sites of the diseases, lower side effect, and improve pharmacological effect. The aim of this project is to utilize particle engineering technology to improve the efficacy of inhaled products by improve lung deposition, modulating dissolution rates and absorption of inhaled drugs. This project can be carried out at University of Sydney or Shenyang Pharmaceutical University, China.

**Supervisor: Mingshi Yang**

**Spray-dried protein formulations**

The spray-drying process may be less expensive, but more efficient to process proteins or peptides as compared to other drying techniques. This technique has additional potentials in not only stabilization of the proteins but also engineering the protein formulations into dry particles for various pharmaceutical applications, e.g. **inhalable, injectables, and oral administration**. This project is intended to investigate the influence of formulation and process variables in the spray-drying process on particle characteristics and physicochemical stability of the protein formulations. This project can be carried out at Novo Nordisk.

**Supervisor: Mingshi Yang**

**Electrospraying/Electrospinning in pharmaceutical application**

Electrospraying/Electrospinning are emerging technologies in the pharmaceutical filed to fabricate micro/nano-structured materials for drug delivery and tissue engineering. This project aim to explore the application of this technology and investigating to promote this technology in the pharmaceutical field for producing **orodispersible films, wound dressing, and injectable depot microparticles**.

**Supervisor: Mingshi Yang**
**Anders Østergaard Madsen**  
Associate Professor  
Building 13, floor 7, room 705  
a.madsen@sund.ku.dk  

**Research focus:** Crystallography, pharmaceutical materials science, synchrotron-based techniques, computational pharmaceutics.

### Examples of projects

#### Anhydrate-hydrate systems in pharmaceutical products

During production and storage of solid state dosage forms the role of hydrate formation cannot be underestimated. The transformation between hydrates and anhydrates occurs as a function of temperature and humidity, and severely affects the properties of the crystals.

The aim of this project is to understand how the water activity level and the temperature can influence the ratio of the anhydrate and hydrate forms of different model compounds, and how the properties of the bulk material changes as a consequence of these transformations.

**Supervisors:** Anders Ø. Madsen, Jukka Rantanen

#### Co-crystals for crossing the blood-brain barrier

It is notoriously difficult to treat disorders in the central nervous system, because most molecules cannot reach the brain due to the blood-brain barrier. In this project, you will work on designing, making and characterizing the properties of co-crystals consisting of several drugs that will work together to cross the barrier and maintain the drugs in the brain.

**Supervisors:** Anders Ø. Madsen
6 Microscale Analytical Systems Group

https://pharmacy.ku.dk/research/microscale-analytical-systems/

List of potential thesis supervisors:

<table>
<thead>
<tr>
<th>Name</th>
<th>Title</th>
<th>Building, Floor, Room</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jörg P. Kutter</td>
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</tr>
</tbody>
</table>

Short description of research field:

Our research group provides analytical chemical tools for tackling many challenges in pharmaceutical and medical research, especially in situations where sample size is limited, where the molecules of interest are only present in small concentrations, or where a large number of sample needs to be processed in a short time frame. To enable this cutting-edge analysis we develop and apply technologies such as micro-nano engineering, microfluidics, and polymer science for next generation high-throughput workflows, e.g., in protein characterization, peptide analysis, drug transport studies, and drug delivery.

Main focal areas of the group are modern separation techniques (e.g. LC, CE) coupled to mass spectrometry, advanced sample preparation methods (e.g., µSPE, µEME), traditional spectroscopic techniques (e.g., NMR, IR, Raman) and a range of microfluidics-driven techniques (e.g., droplets, micro-nano particle fabrication); furthermore, we apply ex vivo models and develop microphysiological in vitro models (i.e., organ-on-a-chip) that are all intended to understand drug-target interactions, investigate drug metabolism, and getting insight into disease progression and therapeutic efficacies.
Jörg P. Kutter  
Professor  
Building 17, 5th floor, room 504B  
jorg.kutter@sund.ku.dk  

**Research focus:** Microfluidic devices for bioanalytical challenges in pharmaceutical and related life sciences

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**Examples of projects**

<table>
<thead>
<tr>
<th>Lab-on-a-Chip for next-generation sample separation and analysis</th>
</tr>
</thead>
</table>
| The analysis of complex protein mixtures is of tremendous importance for pharmaceutical drug discovery. To identify potential drug targets, complex mixtures such as blood, cell cytoplasm or secretome have to be screened. High-throughput screenings involve large numbers of samples and compounds, which are, however, only available in small amounts. Therefore, the sample preparation has to be miniaturized, integrated and automated. Ideal platforms to meet these requirements are microfluidic devices, which allow the precise control of chemical reactions and the integration of other functional elements (so-called lab-on-a-chip). For instance, microchip liquid chromatography provides high separation efficiency, resolution, and sensitivity. During such a project, a microscale device capable of chromatographic separation will be further developed to enable direct coupling to highly sensitive analytical methods, such as mass spectrometry (MS).  

*Supervisors:* Jörg P. Kutter, Nickolaj J. Petersen |

<table>
<thead>
<tr>
<th>Advanced sample preparation methods on microfluidic chips</th>
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</thead>
</table>
| Analysis from complicated matrices (i.e., cell cultures) requires advanced sample preparation tools. This is particularly challenging when small sample volumes are involved. Here, we develop techniques such as electro-membrane extraction to, e.g., monitor drug transport through cell-based models of natural barriers (so-called organ-on-a-chip systems).  

*Supervisors:* Jörg P. Kutter, Nickolaj J. Petersen, Stig Pedersen-Bjergaard |
**Claus Cornett**  
Assoc. Professor  
Building 17, 5th floor, room 511  
claus.cornett@sund.ku.dk

**Research focus:** Quantitative analysis of pharmaceutical compounds from plants; human metabolism and drug validation

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**Title Quality assurance and development of Plant medicine**

Focus will be on characterizing plant based raw materials. Earlier and ongoing projects have been centered around Cannabis and Quinine, a current project (funded by DANIDA) is studying *Synadenium glaucescens* from Tanzania.

BYOP (Bring Your Own Plant...), if you have a special interest in a plant medicine, and access to plant material, let’s negotiate.

Analytical methods used: HPLC-UV, HPLC-MS, GC-MS and NMR.

**Supervisors:** Nickolaj Petersen and Claus Cornett  
**No of students:** 1-2

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**Streamlining the grasshopper in vitro model**

Finding human drug metabolizing enzymes in other species, such as insects, can reduce the number of animal experiments in pre-clinical trials in drug discovery and development. Within this project, you will work with the grasshopper *Schistocerca gregaria*, to find relevant drug metabolizing enzymes in the grasshopper’s “blood” – the hemolymph. You will learn, how to inject drug compounds into the grasshopper and how to collect samples, and how to set up and run enzyme assays, and how to prepare these samples for instrumental analysis with LC-MS or UV detection. Finally, you will be able to evaluate drug metabolism in the grasshopper’s hemolymph and conclude on the relevance of your findings for the grasshopper model in early drug discovery and development.

Analytical methods used: HPLC-UV, HPLC-MS, GC-MS and NMR.

**Supervisors:** Nickolaj Petersen and Claus Cornett  
**No of students:** 1-2
Grasshopper model for drug permeation and metabolism studies in brain

Small animal models are a tool in early drug discovery to predict drug uptake and metabolism. Recently, the grasshopper *Schistocerca gregaria* has been introduced as a model to investigate drug uptake and metabolism in the grasshopper brain. In order to optimize throughput we will investigate the feasibility of using frozen grasshopper brains, as the excision of the brains is time consuming, so the possibility of using previously frozen brains would enable well-plate methods or microanalytical methods.

Analytical methods used: HPLC-UV, HPLC-MS

**Supervisors: Nickolaj Petersen and Claus Cornett  No of students: 1-2**

Capillary electrophoresis coupled to MS

Capillary electrophoresis (CE) provides great potential for a wide range of molecular formats, from small peptides to proteins, DNA and nucleotides. With CE-MS analysis, information about the degradation pathways, post-translational modifications and process-related impurities could be acquired which would otherwise be difficult to obtain with LC-MS.

Samples from Novo Nordisk that have been stress tested for stability will be investigated to compare advantages and limitations compared to traditional LC-MS.

Analytical methods used: CE-MS, HPLC-MS

**Supervisors: Nickolaj Petersen  No of students: 1**
The main purpose of the Pharmaceutical Physical and Analytical Chemistry (PPAC) Group is to develop novel approaches for physical chemical characterization of drugs and delivery systems. The work paves the way for design of effective novel medicines and a better understanding of the fate of drug substances and delivery systems through application of quantitative analytical methods.

The PPAC group applies physical chemical approaches in combination with advanced analytical techniques (ICP-MS, SAXS, UV-Imaging and Taylor dispersion analysis) to advance understanding of fundamental processes in drug design, development and characterization. Common to the activities is a focus on the interplay between basic physical chemical properties of drug substances and excipients, kinetics and transport processes in relation to both drug delivery and analytical methods.

Keywords: analytical chemistry, cubosomes/hexosomes, drug delivery, excipients, injectables, in vitro release, LC-ICP-MS, metallo-drugs, nanoparticles, preformulation, SAXS, Taylor dispersion analysis

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Physical chemical characterization of drug substances and delivery systems.
Development of methods for physical chemical characterization, transport studies, in vitro release and dissolution testing (e.g., UV imaging, capillary electrophoresis (CE), Taylor dispersion analysis (TDA)). Molecular interactions. Study of non-covalent interactions of drug substances and development of affinity methods based on affinity CE and TDA. Characterization and development of drug delivery systems for cutaneous administration. Development of parenteral depot formulation principles (intra-articular and subcutaneous administration), e.g., for treatment of osteroarthitis. Kinetics. In relation to drug transport processes as well as chemical kinetics and stability testing. Design of prodrugs. Optimization of pharmacokinetics of drug substances by bioreversible derivatization.

Examples of projects

**Characterization of nanoparticulate drug delivery systems**

Nanotechnology is widely used in the development of new drug therapies. However, significant challenges related to characterization and development remains. This project focuses on the development of new methods to characterize nanoparticulate drug delivery systems, e.g. liposomes, cubosomes, nanocrystals. Traditional analytical chemical procedures are not well-suited for characterization and analysis of these drugs. New methods based on capillary electrophoresis, Taylor dispersion analysis and UV imaging will therefore be developed. It is of paramount importance that the methods require limited amount of sample as the new nanoparticulate drug delivery systems are usually only produced in small quantities. The methods will allow us to address critical parameters such as incorporation efficiency, release, non-covalent interactions, aggregation and adsorption.

**Supervisors:** Jesper Østergaard, Henrik Jensen and Bente Gammelgaard

**Novel in vitro drug release models for predicting in vivo performance of injectables**

The aim of the project is to develop novel in vitro release testing methods suited for predicting the in vivo fate of injectables. Such methods are of importance in the development of future drugs for subcutaneous, intramuscular or intra-articular injection. We intend to combine a thorough understanding of the transport processes occurring at the injection site with efficient characterizing techniques for unravelling drug release mechanisms and predicting the biological fate. The ultimate validation will be the establishment of an in vitro

**Supervisors:** Jesper Østergaard, Susan Weng Larsen and Henrik Jensen

**Compound screening in early drug development using real-time surface dissolution imaging**

Surface dissolution imaging provides new opportunities for visualization and study of drug dissolution mechanisms. The aim of the project is to identify and establish best practices in UV imaging-based dissolution testing. The work will involve development of new UV imaging methods for selected test compounds. The project may involve an internship at external partner.

**Supervisors:** Jesper Østergaard

**Thesis projects on pharmaceutical analysis with pharma industry or hospital pharmacy**

Ask for current possibilities.

**Supervisors:** Jesper Østergaard
### Henrik Jensen, Associate Professor
Email: henrik.jensen@sund.ku.dk

My research is mainly focused on developing new analytical methodologies for characterization of drugs and drug formulations. The primary focus has been on miniaturization as well as automation of analytical protocols. We often rely on capillary based approaches, but recently we are further developing the methods into wearable sensors for monitoring drugs and their unwanted side effects. Most of my former master thesis students are employed in the pharmaceutical industry, amongst others in the spin-out company FIDA-Tech which is based on research in the group.

### Examples of projects

<table>
<thead>
<tr>
<th>Project</th>
<th>Description</th>
<th>Supervisors</th>
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<tr>
<td><strong>FIDA: A new approach for biomarker quantification and immunogenicity assessment</strong></td>
<td>Protein based biomarkers may be used to determine the most optimal drug treatment as well as to monitor treatment status. Therapeutic monitoring of drug compounds is in many cases also beneficial for a successful treatment and recovery. In this project Flow Induced Dispersion Analysis (FIDA) will be investigated for biomarker and immunogenicity assessment. The project may involve internal as well as external collaborations.</td>
<td>Henrik Jensen and Jesper Østergaard</td>
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<tr>
<td><strong>Management of Biopharmaceuticals and Immunogenicity using Wearable Devices</strong></td>
<td>Wearapeutics are wearable devices that can detect biomarkers, monitor and/or deliver a medical treatment and therefore can be the central component of an individualized therapy. At present, the cross disciplinary solutions necessary to realize a widespread application of wearapeutics in individualized therapy are in their infancy and true wearables have only recently been demonstrated for simple sensor systems. In this project, we aim to develop new sensing technologies for biologics (protein based drug compounds) to be used in wearables. The new approaches will be compatible with the small volumes extracted from the subcutaneous environment and will thus rely on capillary electrophoresis, Flow Induced Dispersion Analysis (FIDA) and electrochemistry. The new methodologies will be tested using an in vitro model of wearapeutics for subcutaneous administration. Ultimately, the developed solutions will be adaptable for use with wearable electronics such as smartphones or smart watches.</td>
<td>Henrik Jensen and Jesper Østergaard</td>
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<tr>
<td><strong>Stability assessment of protein based drugs</strong></td>
<td>In this project, the FIDA methodology (see project above) is utilized for stability assessment of protein based drugs. While protein based drugs have proven efficient for the treatment of a range of serious diseases, a number of challenges remains in developing and formulating these drug compounds. Notably, they are known to be structurally labile and efficient methods for assessing stability are currently suboptimal. In this project we take advantage of the fact that structural changes can be monitored as size changes, change in optical properties and altered function (binding ability).</td>
<td>Henrik Jensen</td>
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**Examples of projects**

### BRAIN-PENetrating cubosomal and hexosomal NANOcarriers for glioma-targeting delivery

This project focuses on the formulation of immune-safe non-lamellar liquid crystalline nanocarriers for bioimaging of - and concomitant drug delivery to - cancerous brain tumors.

**Supervisors:** Anan Yaghmur

### Cubosomes and hexosomes as novel nanocarriers for loading anticancer drugs

The formation/characterization of nanocarriers based on *cubosomes* and *hexosomes* for delivery of anticancer drugs

**Supervisors:** Anan Yaghmur

### Microfluidic platforms for the production of monodispersed cubosomes & hexosomes

Combining SAXS to a microfluidic device for the structural characterization of monodispersed drug nanocarriers based on lipid nanoparticles

**Supervisors:** Anan Yaghmur, Aghiad Ghazal

### Self-assembled liquid crystalline nanostructures as sustained release injectable formulations

The use of non-lamellar liquid crystalline phases as drug delivery systems for intra-articular or subcutaneous administration appear attractive due to the sustained release capability. Combination of biophysical investigations with in vitro release studies

**Supervisors:** Anan Yaghmur & Susan Weng Larsen
### Research focus:
Investigation and application of physicochemical approaches to improve understanding of processes in drug delivery including parenteral depot design, profiling of drugs and analytical approaches for *in vitro* release testing. Research projects are related to i) development of parenteral sustained release drug delivery systems including *in situ* suspension-forming injectables, in situ formed liquid crystalline nanostructures and prodrug approaches and ii) development and utility of *in vitro* release methods to predict *in vivo* performance of depot formulations for the subcutaneous and intra-articular route of administration.

#### Examples of projects

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<td><strong>Local and sustained co-delivery of drugs to improve outcomes following joint replacement</strong>&lt;br&gt;To improve pain management and prevent infections related to joint replacement surgery, there is a need for efficient drug delivery systems (DDSs) that can maintain and sustain an optimal therapeutic level of multiple drugs at the surgical site. The current project focuses on rational design of parenteral <em>in situ</em> forming DDS based on lyotropic non-lamellar liquid crystalline phases for co-delivery of drugs. The drug substances are incorporated in lipids, which self-assemble upon contact with the tissue fluid to form well-ordered inverted type nanostructures (bi-continuous cubic and hexagonal phases). The aims of the project are to i) study incorporation of model drugs with different physicochemical properties in these systems and ii) investigate drug release characteristics from <em>in situ</em> formed liquid crystalline phases. Various <em>in vitro</em> release methods as well as the presence of biologically relevant fluid will be used to characterize events influencing the sustained release properties.</td>
<td>Susan Weng Larsen, Anan Yaghmur and Jesper Østergaard</td>
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<tr>
<td><strong>A novel prodrug principle to achieve localized and sustained NSAID action after joint injection</strong>&lt;br&gt;Orally administered NSAIDs are intensively used in the treatment of osteoarthritis for pain management and reduction of inflammation. However, oral NSAIDs may evoke severe side effects even after short term use which constitutes impediments to their use. Following direct injection into the injured joint, a high therapeutic NSAID concentration can be accomplished while minimizing systemic adverse effects. As NSAIDs disappear rapidly from the synovial space (half-lives of 0.5–6 h), depot strategies are needed. In the current project, a prodrug-based <em>in situ</em> suspension-forming system intended for localized and sustained NSAID action upon intra-articular injection will be investigated. The project relates to characterization of synthesized NSAID prodrugs and will include: (i) solubility in aqueous buffers and in synovial fluid, (ii) pH dependent stability, (iii) sensitivity to enzymatic cleavage (plasma and synovial fluid), (iv) affinity to proteins and (v) rate of NSAID release from prodrugs using an <em>in vitro</em> release model simulating the joint environment.</td>
<td>Susan Weng Larsen and Jesper Østergaard</td>
</tr>
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<td><strong>Design of <em>in vitro</em> drug release models for predicting <em>in vivo</em> performance of depot injectables</strong>&lt;br&gt;Development of <em>in vitro</em> release models for quality control as well as formulation design purposes is a critical activity in the characterization of parenteral depot formulations. Ideally, an <em>in vitro</em>-<em>in vivo</em> correlation should be established, however, it requires that the drug release mechanism is the same <em>in vitro</em> and <em>in vivo</em>. The project focuses on characterizing drug release from sustained release formulations for subcutaneous and/or intra-articular administration. The aim of the project is to develop <em>in vitro</em> release models to achieve in depth understanding of how formulation designs as well as physiological parameters influence drug release mechanism and rate and drug transport the blood capillaries.</td>
<td>Susan Weng Larsen, Jesper Østergaard and Henrik Jensen</td>
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Our research aims at exploring the application potentials of functional excipients based on a better understanding of excipient effects on drug release and absorption, as well as interactions between excipients and drug molecules. We use both lipids and polymeric excipients, and are especially interested in lipid excipients due to their versatility and stability, as well as the potential in controlling drug release. The main research activities include designing and characterizing drug carriers such as solid lipid particles and hybrid particles, optimizing formulations for specific applications, and developing in vitro models to evaluate formulations with sustained drug release properties.

### Examples of projects

#### Functional excipients and drug delivery

Excipients play an essential role in drug delivery. Lipid-based formulations can increase the bioavailability of lipophilic drugs by improving drug dissolution and permeation. Both solid lipid particles and polymeric particles are good carriers for sustained drug delivery, but the mechanism of drug release from those particles are different. Hybrid polymer-lipid particles provide better effect in sustained delivery of drugs due to synergistic effect of polymer and lipids. The project aims at evaluating effect of excipients and particle preparation methods on drug release kinetics in order to design efficient drug carriers for specific applications via different administration route.

**Supervisor:** Huiling Mu

#### In vitro models to evaluate formulations for sustained drug delivery

Understanding the release kinetics of drugs from particles is a fundamental prerequisite for efficient design of microcarriers for sustained drug delivery. However, there is no suitable method available to assess formulations with sustained drug release properties in vitro. The project aims at establishing bio-relevant *in vitro* models using hydrogel-based soft tissue surrogates addressing *in vivo* conditions including pH, temperature, and matrix composition.

**Supervisors:** Huiling Mu and Jesper Østergaard

#### Bioadhesive formulations for local mucosal drug delivery

Solid lipid formulations can be used for sustained drug delivery. Incorporation of functional excipients in the formulations may create extra application potentials and be used to improve local therapeutic effect by adhesion to the mucosal surfaces (e.g. mouth, eye). The project aims at investigating the potential of combining bioadhesive excipients and lipid particles and validating the bioadhesive properties of the formulations *in vitro*. Nanoparticles, prepared by hot melting and probe sonication method, will be incorporated into buccal films or hydrogels, hence testing drug encapsulation efficiency, drug release, bioadhesion and *ex vivo* drug permeation.

**Supervisors:** Huiling Mu and Jette Jacobsen
Our general research interest is to develop and apply advanced analytical techniques for exploration of novel drug delivery systems and gain knowledge of the uptake, distribution, and metabolism of inorganic and bioinorganic molecules and drugs in biological systems. To pursue this interest we apply LC-ICPMS, CE, and LCMS.

Examples of projects

**Antibacterial Nanoparticles - characterization of nanoparticulate drug delivery systems**

Among the most promising novel antibiotic agents are metal nanoparticles, which have shown strong antibacterial activity in numeral studies. Ag is the most commonly applied nanoparticle metal owing to its ancient use as antibacterial agent, but other metals like Au, Cu, Fe, Si, and Ti are frequently used. Owing to their large surface to volume ratio, nanomaterials possess distinct physicochemical properties, which influence their effect in the organism. The most important characteristics are composition, concentration, size and size distribution, protein interaction, surface charge and release of ions from the metal.

The focus of these projects is determination of size and concentration by single particle inductively coupled plasma mass spectrometry (SP-ICP-MS). Standards of selected model nanoparticles with different physicochemical properties are used to develop and validate the SP-ICP-MS technique. The methods are applied to authentic nanoparticulate systems received from collaborators. Each project will focus on determination of size and size distribution in standards and quantification in human plasma of a particle system chosen among Ag, Au, FeO, Se, Si, and TiO₂. The projects are the basis for future research on the interaction of nanoparticles in biological systems.

**Supervisor:** Bente Gammelgaard, Laura Hyrup Møller, Stefan Stürup

**Projects at Department of Forensic Medicine (External project)**

1) Examination of drugs and drugs of abuse in alternative matrix

2) Application of automated pipetting robots in forensic chemistry

3) Use of informatics and statistical methods for optimization and quality control in forensic chemistry

**Supervisors:** Bente Gammelgaard and external supervisor

**Projects at National Research Center for the of Working Environment (External project)**

1) Method development for detection of organophosphate ester metabolites in urine using LC-MS-MS for biomonitoring studies

2) Dermal uptake of PCBs using an ex vivo skin model

3) Method development for pesticide metabolites in urine using LC-MS-MS and analysis of samples from farmers in Uganda

**Supervisors:** Bente Gammelgaard and external supervisor
Our general research interest is to develop and apply advanced analytical techniques for exploration of novel drug delivery systems and gain knowledge of the uptake, distribution, and metabolism of inorganic and bioinorganic molecules and drugs in biological systems. To pursue this interest we apply LC-ICPMS, CE, and LCMS.

Examples of projects

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### Examples of projects

**Antibacterial Nanoparticles - characterization of nanoparticular drug delivery systems**

Among the most promising novel antibiotic agents are metal nanoparticles, which have shown strong antibacterial activity in numerical studies. Ag is the most commonly applied nanoparticle metal owing to its ancient use as an antibacterial agent, but other metals like Au, Cu, Fe, Si, and Ti are frequently used. Owing to their large surface to volume ratio, nanomaterials possess distinct physicochemical properties, which influence their effect in the organism. The most important characteristics are composition, concentration, size and size distribution, protein interaction, surface charge and release of ions from the metal.

The focus of these projects is determination of size and concentration by single particle inductively coupled plasma mass spectrometry (SP-ICP-MS). Standards of selected model nanoparticles with different physicochemical properties are used to develop and validate the SP-ICP-MS technique. The methods are applied to authentic nanoparticulate systems received from collaborators. Each project will focus on determination of size and size distribution in standards and quantification in human plasma of a particle system chosen among Ag, Au, FeO, Se, Si, and TiO$_2$. The projects are the basis for future research on the interaction of nanoparticles in biological systems.

**Supervisor:** Bente Gammelgaard, Laura Hyrup Møller, Stefan Stürup

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**Determination of trace element impurities in drug products (External project)**

This project entails development and validation of new ICP-OES based analytical methods to comply with Pharmacopoeia requirements for elemental impurities. The project is a collaboration with Lundbeck Pharma A/S.

**Supervisors:** Stefan Stürup

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**UHPLC-ESI-MS/MS for quantification of isotope labeled metabolites**

Development and validation of a UHPLC-ESI-MS/MS method for quantifying of isotope labelled glucose metabolites such as citrate, succinate, glutamate and glutamine. The final method will be applied for determination of isotopologues in cell samples.

**Supervisors:** Stefan Stürup, Laura McNair (ILF), Blanca Garcia (ILF)
8 Protein Analysis

Group Leader
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Homepage: https://pharmacy.ku.dk/research/protein-analysis-group/
Group news: https://proteinanalysis.sites.ku.dk/

The vast majority of drugs work by binding to and changing the function of proteins in the human body. Furthermore, many new drugs are themselves protein-based (so-called biopharmaceuticals) and these complex drugs account for the most rapidly growing drug in the pharmaceutical industry. Analysis of proteins is therefore at the core of pharmaceutical research.

Through the thesis projects below, you can get hands-on laboratory experience of how to work with proteins and learn state-of-the-art techniques for detailed analysis and characterization of protein-drug targets and biopharmaceuticals (protein chemistry, biophysics, liquid chromatography and mass spectrometry).

Our research centers around the use of mass spectrometry to provide the critical information concerning quantity, quality, structure and interactions of proteins - which is needed to guide and develop new and improved drugs. In particular, we have world-leading expertise with the HDX-MS technique, an incredibly sensitive method for studying the conformation, dynamics and interactions of proteins.

Examples of publications involving past master thesis projects:

**Kasper D. Rand, Professor MSO, Ph.D.**  
Email: kasper.rand@sund.ku.dk  
Room: 18.4.404  
Telephone: 23712556  
[http://research.ku.dk/search/?pure=en/persons/130972](http://research.ku.dk/search/?pure=en/persons/130972)  
**Research focus:** Protein Analytical Chemistry, HDX-MS (& see above)

### Examples of projects

#### Structural analysis of biopharmaceuticals

Analysis of the primary and higher-order structure of protein-based drugs is critical for both understanding molecular action as well as monitoring and comparing drug product quality. In this suite of projects, you will apply a new powerful analytical technology that uses mass spectrometry to measure the hydrogen/deuterium exchange of proteins in solution (HDX-MS) and is thus capable of producing detailed information on the structure of biopharmaceuticals. You will use this technique to analyze and compare the structural properties of new potential protein drugs in development and thus help provide a critical molecular understanding of their pharmaceutical properties and function in the human body. Work will be done in close collaboration with researchers at UCPH or industrial collaborators such as Biogen Idec (USA), Roche (Germany) and Novo Nordisk (Denmark), depending on the project. There is typically also the possibility to perform parts of the project at the industrial collaborator. **No. of students: 1-2**

#### Understanding the binding of drugs to target proteins of the human body

HDX-MS is a very sensitive method to study the binding of small molecule ligands or large protein-based drugs to naturally occurring protein receptors in great detail. By using mass spectrometry, we measure the hydrogen/deuterium exchange (HDX-MS) of the protein receptor in the absence and presence of a single or a panel of potential ligands. We can thus map the binding site of ligands on the protein receptor and study the structural effects of binding. In this project, you will use HDX-MS to study both the binding of ligands (small molecule or large protein-based) to important new pharmacologically interesting protein receptors. Work will be conducted in collaboration with academic/industry collaborators. **No of students: 1-2**

#### Coupling microfluidics and mass spectrometry for improved analysis of proteins

Analysis of protein drugs requires specialized sample treatment and advanced analytical techniques as they are large and complex and often contain modifications (e.g. glycosylations, disulfide bonds). In this suite of projects, we explore the use of microfluidic chips to perform rapid and automated preparation of protein samples (sample concentration, enzymatic reactions, chromatographic separation) for analysis by mass spectrometry. You will learn how to implement protein chemistry and liquid chromatography on a microfluidic device coupled to state-of-the-art protein analysis by mass spectrometry. The project will be done with co-supervision from Jorg Kutter of the Microscale Analytical Systems group. **No of students: 1-2**
List of potential thesis supervisors:

**Jette Jacobsen**  
Associate Professor  
Building 13, 5th floor, room number 543  
jette.jacobsen@sund.ku.dk

**Daniel Bar-Shalom**  
Associate Professor  
Building 13, 5th floor, room number 514  
daniel.barshalom@sund.ku.dk

**Ragna Berthelsen**  
Assistant Professor  
Building 13, 7th floor, room number 718B  
ragna.berthelsen@sund.ku.dk

**Anette Müllertz**  
Professor  
Building 13, 7th floor, room number 708  
anette.mullertz@sund.ku.dk

Short description of research field:

In the Physiological Pharmaceutics group (PhysioPharm) we work with oral and mucosal drug delivery. We develop novel drug delivery systems (DDS) to improve drug bioavailability and/or to ensure the maximal therapeutic effect with fewest possible side-effects. We work with both poorly soluble drugs and peptides, and focus on lipid-based DDS and customized release. We develop DDS for special populations (e.g. children; the elderly and patients with hypochloridria or inflammatory bowel disease). We use *in vitro* models of the mouth, eye and the gastro-intestinal (GI) tract that we are continuously improving in order to make them as physiologically relevant, and predictive for bioadhesion, dissolution, release and permeation, as possible. In addition, we also use and develop *in silico* models to further understand the absorption and metabolism of the drug.

**Note 1:** As a general rule, a co-supervisor will be allocated to each master student, often a PhD student from the PhysioPharm Group, or a person from the industry or from other institutions.

**Note 2:** All of us have close contact to the industry and other universities – so come talk with us if you desire a master project in the industry – or abroad.
**Jette Jacobsen**  
Associate Professor, Cand.Pharm., PhD.  
Building 13, 5th floor, room 543, jette.jacobsen@sund.ku.dk  

**Research focus:** Mucosal drug delivery, oromucosal (buccal, sublingual), ocular, bioadhesion, ex vivo permeation, liquid-semi solid-solid formulations, xerostomia

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### Examples of projects

**In vitro in vivo correlation of oromucosal lubrication and bioadhesiveness**

- Of selected polymers with different physico-chemical properties (charge, molecular size, chemical structure, HLB) aiming at a platform for screening of oromucosal bioadhesiveness. Today, human in vivo studies of oromucosal bioadhesion are sparse. Examples of qualitative and quantitative in vitro bioadhesion methods to be validated in this project: Zeta potential, tissue-based tensile strength, rheology, tissue-based retention model, turbidity, contact angle. Initially, an application to authorities for study of human in vivo oromucosal bioadhesiveness must be written.

**Supervisors:** Jette Jacobsen

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**Rule of ## for buccal and sublingual drug absorption to systemic delivery**

This project aims at elucidating the optimal physico-chemical properties of drugs for buccal or sublingual absorption. A series of drugs will be evaluated with regard to solubility in saliva and permeability (cell cultures or ex vivo animal mucosa in side-by-side diffusion cells (e.g. sublingual or buccal mucosa). The project may be planned in collaboration with pharmaceutical industrial partner.

**Supervisors:** Jette Jacobsen

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**Safety and enhancement of oromucosal or ocular drug permeability**

These projects aim at evaluating excipients (e.g. absorption enhancers, bioadhesive polymer, co-solvents, buffering pH, surface active preservatives, flavours ect.) to gain a mechanistic knowledge of in vitro mucosal permeability of drugs with different physico-chemical properties by employing physiological relevant transport studies with cell cultures or ex vivo animal mucosa in side-by-side diffusion cells (e.g. sublingual or buccal mucosa, and cornea). Potential formulations are liquids (e.g. original product and generics), drugs printed on bioadhesive films (for individualized personal medicine) or solids. The projects may be planned in collaboration with pharmaceutical industrial partner and Chr. Janfelt to perform high-resolution MALDI mass spectrometry imaging of drugs and excipients.

**Supervisors:** Jette Jacobsen, Miriam Kolko (ILF), Susan Weng Larsen, Natalja Genina, Christian Janfelt

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**Bioadhesive formulations for alleviation of xerostomia**

Xerostomia (dry mouth) can be a very disabling state of health. Xerostomia can be due to e.g. use of medicine or illness (Sjögrens syndrome, radiation therapy in cancer). We hypothesize that each, salivary proteins and lipids, contribute to maintain functions of saliva in bulk and at the mucosal surface. The projects will focus on formulation of a physiological relevant composition for daily care and as a drug delivery system. The work may comprise preparation and characterization of semisolid or liquid bioadhesive formulations with and without drugs, development of in vitro cell culture based methods for oromucosal spreadability/wettability (i.e. measurement of single-sided contact angle and surface tension) or friction of formulations, characterization of bioadhesiveness (retention time and force), and mucosal hydration rate. The projects are in collaboration with an external clinical specialist in oromucosal medicine and pathology.

**Supervisors:** Jette Jacobsen, Huiling Mu and Daniel Bar-Shalom
Examples of projects

Development of “instant pudding” vehicles

There are different scenarios requiring different solutions: (a) Individual, single dose commercial products to be produced by the industry, (b) Vehicles to be added to magisterial compounded products at the hospital or community pharmacy and (c) Vehicles for mass treatment in the developing world where a whole village is treated at once (for example, with anti-parasitic combinations) etc. The projects are usually carried out in collaboration with interested parties (pharmaceutical and food industry, raw materials suppliers, analytical instrumentation producers and academic partners. Many of those abroad)

Supervisors: Daniel Bar-Shalom

Paediatric/Geriatric drug delivery.

Children and the elderly are special population groups from the oral drug delivery perspective. Their swallowing (in)abilities are different from those of the “average population” (those able to swallow tablets and capsules). The elderly and chronically sick children tend to take multiple drugs, thereby complicating the treatment. Our approach is to individually microencapsulate the drugs to eliminate the (bad) taste problem, to prevent unfortunate interactions between the drugs when in combination and to provide controlled release, if possible. The microencapsulates are mixed with dry, “instant pudding” formulations, and just before administration water is added, resulting in a pleasant, easy to swallow pudding/applesauce mass.

Supervisors: Daniel Bar-Shalom

Development of the dispensing systems for Microencapsulate/Pudding products

It is not sufficient to have the components of the product, a dispensing strategy and device are needed too. Project in this part involve collaboration with design experts.

Supervisors: Daniel Bar-Shalom

Development of microencapsulated particles for children and elderly

Different applications require different solutions. The drugs used at the hospital are a very heterogeneous group, those given in anti-parasitic treatments are notoriously water insoluble, in single doses and long-term stability is expected.

Supervisors: Daniel Bar-Shalom

Oral controlled release of high dose, highly soluble drugs

The problem of insoluble drugs is much researched all over the world, including people in our own department. The opposite problem has been largely ignored, but it is there and represents an interesting “niche”.

Supervisors: Daniel Bar-Shalom
Ragna Berthelsen
Assistant Professor
Building 13, 7th floor, room 718B, ragna.berthelsen@sund.ku.dk

Research focus: Human gastro-intestinal physiology. Design and development of predictive in vitro models, simulating the gastro-intestinal tract. Use of in vitro models to evaluate oral drug performance, and formulation design, as well as to study and to understand mechanisms of drug solubilization and absorption. Special focus on drug delivery to the pediatric population.

Examples of projects

Development a combined gastrointestinal digestion and permeation in vitro model.

In order to achieve a systemic response following oral administration, a given drug needs to dissolve (or be solubilized) in the gastrointestinal (GI) fluids and permeate the intestinal mucosa to reach the systemic circulation. As many poorly water soluble drugs are affected by the co-administration of food, or formulated in a lipid based drug delivery system to ensure GI drug solubilization, the GI digestion processes will affect the drug absorption. Therefore, two key parameters to evaluate in order to predict the in vivo performance of orally administrated poorly water soluble drugs are the drug solubilization during GI digestion and the permeation across the intestinal mucosa. As these two processes affect each other, a predictive in vitro model needs to mimic both processes simultaneously. The purpose of the present master’s thesis project is to develop and evaluate a combined GI digestion and permeation in vitro model.

Supervisors: Ragna Berthelsen, Mette Klitgaard (phd student) and Anette Müllertz

Lipid based drug delivery systems for the pediatric population

As the pediatric population differs from the adult population in many aspects, the design of drug delivery systems (DDS) for the pediatric patient requires careful considerations. In oral administration, the physiological conditions of the gastro-intestinal tract is so complex that the rate and extent of drug absorption are influenced by many factors, especially when the drug solubility is low, it often causes incomplete absorption and low bioavailability, seriously affecting the drugs clinical efficacy and the treatment of the disease.

The project may involve: 1) construction of a pediatric lipid based DDS, and 2) In vitro evaluation of the designed DDS, studying drug solubilization capacity and mechanism, stability and drug release profiles using in vitro pediatric digestion model, and 3) studies of the permeation of poorly soluble drugs following administration of the designed DDS.

Supervisors: Ragna Berthelsen, Anette Müllertz, and Xioana Lui (phd student)

Is intestinal mucus an important factor in solubilization and absorption of poorly soluble drugs?

Efficient oral therapy is dependent on a good and reproducible drug absorption. However, many active drug candidates suffer from poor water solubility, which makes it difficult to formulate them into delivery systems with high and reproducible bioavailability. One important factor influencing this, is the poor understanding of the actual conditions in the gastrointestinal tract, and the factors that are limiting for the drug absorption. Therefore, the tools that are used in the development process are in many cases not predictive for the in vivo situation. One example is the media that are used for predicting the drug dissolution in the intestine, which often underestimates the in vivo dissolution. We hypothetize that the intestinal mucus layer has a larger solubilization capacity than the intestinal fluids and is therefore a major player in the absorption mechanism for poorly water soluble drugs. Thus, the mucus layer need to be included in in vitro models simulating drug dissolution and absorption.

This project aims to elucidate the impact of the intestinal mucus layer in dissolution, solubilization, diffusion and absorption of poorly water soluble drugs. The project will be directly linked with the current PhD project of Mette Klitgaard.

Supervisors: Mette Klitgaard (PhD student), Anette Müllertz, Jette Jacobsen, Ragna Berthelsen
Anette Müllertz
Professor
Building 13, 7th floor, room 708, anette.mullertz@sund.ku.dk

Research focus: Development of predictive in vitro models, based on human or rat gastrointestinal physiology. Lipid-based drug delivery systems. Small-scale methods to evaluate solubility, dissolution and supersaturation propensity of drugs. Application and development of in silico PBPK models to evaluate release effect on pharmacokinetics.

Examples of projects

Development of a targeted drug delivery system by use of micro-containers
Inflammatory bowel disease (IBD) affects more than 50,000 people in Denmark. Current treatment options are not effective and are often associated with severe side effects due to systemic uptake of the drug. A potential oral drug delivery system (DDS) for treatment of IBD is micro-containers. They provide protection of the loaded drug from both low pH and enzymatic degradation while ensuring unidirectional release in the intestine. The aim is to develop a DDS that targets only inflamed areas of the gastrointestinal tract in IBD patients. This can be achieved e.g. by functionalization of the polymer lid and/or targeting ligands. Newly developed DDS will be tested in vitro, and the promising DDS will be investigated in vivo in a preclinical IBD rodent model.

Supervisors: Anette Müllertz, Thomas Rades & Maja Nørgaard Kristensen (PhD student)

The effect of gastric transfer rate on supersaturation and precipitation of poorly water soluble weak bases
A large solubility difference in the low pH stomach and neutral pH small intestine is a challenge for many new drugs. This solubility difference can lead to supersaturation and subsequent precipitation in the small intestine. This can lead to a large variability in pharmacokinetic studies. Supersaturation is an unstable system, where the concentration of a compound exceeds the (thermodynamic) solubility and over time will precipitate. The aim is to establish a novel two-step dissolution model with a gastric and an intestinal compartment to investigate the effect of gastric transfer rate on small intestinal supersaturation and precipitation of formulations of poorly water soluble weak bases.

Supervisors: Anette Müllertz & Jakob Plum (Post doc, Leo Pharma)

Functionalized self-emulsifying DDS (f-SEDDS) for oral delivery of peptides or proteins
Self-emulsifying drug delivery systems (SEDDS) are solutions of oil, surfactant and co-surfactant spontaneously forming an oil/water emulsion upon mixing with an aqueous medium. SEDDS have shown great potential to improve the bioavailability of peptides by the advantages of mild preparation conditions, protection against enzymatic hydrolysis and build-in permeation enhancement. We will develop functionalized SEDDS (f-SEDDS) with e.g. mucoadhesive properties. F-SEDDS will be characterized by particle size, zeta-potential and in vitro digestion. The performance of the developed f-SEDDS will be evaluated by in vitro cell culture study and in vivo animal models.

Supervisor: Anette Müllertz

Assessing the relation between release profile and pharmacokinetics using PBPK models
Physiologically based pharmacokinetic (PBPK) modelling is important in the drug development process to understand the relation between drug release, absorption and plasma profile. However, there is still shortcomings in the input (absorption) profiles in the PBPK models, e.g. the entire drug solubility profile in the GI tract is not considered. We want to apply PBPK models to different solubility and dissolution profiles, from selected formulations. We will use the softwares GastroPlus and SimCyp.

Supervisors: Anette Müllertz, Ragna Berthelsen, Jakob Plum (Post doc, Leo Pharma)

Simulating food effect on poorly soluble drugs
Many poorly soluble drugs have positive food effect; they have a better bioavailability in the fed state. This is a problem for the reproducibility of the therapeutic effect and it is therefore desired to develop DDS that abolish the food effect. The aim is to develop in vitro models, simulating the fed state GI tract, and by use of this to develop formulations without food effect.

Supervisor: Anette Müllertz
10 Social and Clinical Pharmacy

**Social pharmacy** seeks to have the broad view of medicines in society and focuses on how medicines are perceived, used, and managed by different stakeholders. **Clinical pharmacy** seeks to ensure the optimal and rational use of medicines for the benefit of patients and society through collaboration between pharmacists, other health professionals, and the patient. SCP’s research ultimately seeks to ensure the benefit of medicines for users, organizations, and society. SCP’s research is concerned with the three levels (the user, organization and society) and how they interact to ensure the optimal use of medicines.

Master thesis projects may be connected to existing research projects in the SCP Group, but other relevant ideas for master thesis projects within social and clinical pharmacy are also welcome. If you wish to know more about us and what kind of research we do you can have a look at our homepage (https://pharmacy.ku.dk/research/social-clinical-pharmacy/) and at our WHO collaborating center (https://whocc-meduse.ku.dk). Alternatively, you can use the “Find en forsker” option for members of the research group on the homepage of the University of Copenhagen.

Supervisors in SCP are: Prof. Anna Birna Almarsdóttir, Assoc. Prof: Lourdes Cantarero-Arévalo, Assoc. Prof. Sofia Kälvemark Sporrong, Assoc. Prof. Lotte Stig Nørgaard, Assoc. Prof. Susanne Kaae, Assoc. Prof. Charlotte Vermehren, and Assistant Prof. Ramune Jacobsen.

In addition to these supervisors, SCP has contact to researchers off campus who are willing and able to supervise, eg. at hospital pharmacies, Pharmakon, regional research centers, etc.

We have a coordinated master thesis student system in the SCP Group. First we accept students for the entire group and then we allocate a supervisor to each student. The contacts regarding master theses are lou.cantarero@sund.ku.dk and anna.birna@sund.ku.dk. Please do not write to others in the SCP group with questions about thesis projects.

If you are interested in learning more about writing a master thesis in SCP, you can meet us at the ‘Master thesis day’ on the 25th of October. Here you can talk to us and then sign up on our homepage with relevant information about yourself and motivation for doing a masters project within the SCP research group.

On Monday November 11 we have arranged our own Open House arrangement in the SCP group (UP2, building 10, 4. floor), between 13 and 15. Here you can discuss with us (supervisors and former master thesis students) and have a look at previous master theses. Note, that we do not arrange individual meetings with students. Therefore, if you want to know more – please come by on Monday November 11.

Students selected for master thesis writing in 2021 in our group will be notified in week 47.
11 Solid State Pharmaceutics
https://pharmacy.ku.dk/research/solid-state-pharmaceutics/

The scientific staff consists currently of the three scientists Korbinian Löbmann, Thomas Rades and Holder Grohganz, and a varying number of PhD students.

Short description of the research field:
We develop drug delivery systems based on high-energy solids. The aims are improved stability of the formulations, and solubility enhancement of poorly water-soluble drugs. We furthermore aim to obtain a deeper understanding of the underlying mechanisms for amorphous stability and have a keen interest in novel formulations approaches and novel excipients.

Low solubility is the major challenge for many small-molecule drugs. By stabilizing a poorly water-soluble drug in its amorphous form, its bioavailability can be increased, due to a higher dissolution rate and apparent solubility. Understanding molecular interactions and thereby overcoming the inherent instability of amorphous drugs is one solution to the solubility problem. The amorphous drug can be stabilized with both polymers and small molecules. The amorphous formulation is characterized by a wide range of advanced analytical state-of-the-art methods.

For the production of amorphous formulations of both, small molecules and biomacromolecules, various production techniques, such as ball milling, spray-drying, freeze-drying, microwaves and hot melt processing are applied. Understanding the influence of process and formulation parameters on the solid state of both excipient and drug enables a rational choice of formulation.
**Holger Grohganz**  
Associate professor  
E-Mail: holger.grohganz@sund.ku.dk  
Telephone: +45 35 33 64 73  
Office: 13-6-614

**Research focus** lies in the development of solid dosage forms, including preformulation, formulation, processing and manufacturing together with the relevant solid-state characterization and multivariate analysis. This includes in particular the development co-amorphous systems as well as a deeper understanding of freeze-drying as production technique.

### Examples of projects

**Quality by design (QbD) in the processing of biomacromolecules**

<table>
<thead>
<tr>
<th>Image</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><img src="image1.png" alt="Diagram" /></td>
<td>The quality by design (QbD) principle can be expected to influence the way of pharmaceutical processing in the years to come towards the development of more rational processes. Although, freeze-drying and spray-drying are widely used in peptide and protein formulation, the interaction between various excipients and proteins is not fully understood. This project aims to obtain a deeper understanding of the influence of various composition and process parameters on the solid state form of both novel and established the excipients, and the macromolecule. Analytical techniques may include X-Ray powder diffraction, dynamic mechanical analysis, NIR and Raman spectroscopy as well as the application of multivariate data analysis.</td>
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</table>

**Evaluation of preparation methods for co-amorphous formulations**

<table>
<thead>
<tr>
<th>Image</th>
<th>Description</th>
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<tbody>
<tr>
<td><img src="image2.png" alt="Diagram" /></td>
<td>Low drug solubility is the major challenge for future small molecule drugs. In order to overcome the problematic solubility of BC class 2 drugs, small excipients are investigated to form co-amorphous formulations. Due to the low solubility, ball milling is used as preferred production process. Due to the low capacity of ball mills, other production procedures, such as freeze-drying, spray-drying and hot-melt processing should be evaluated.</td>
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</table>

**Ternary formulations of co-amorphous systems with polymer**

<table>
<thead>
<tr>
<th>Image</th>
<th>Description</th>
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<tbody>
<tr>
<td><img src="image3.png" alt="Diagram" /></td>
<td>The addition of polymeric excipients into co-amorphous systems might possess a potential to improve the dissolution behaviour and stability of co-amorphous systems. Physicochemical properties of formulations are quite easily influenced by different preparation methods. Thus, it is important to investigate the influence of various preparation methods on the final ternary formulation. Relevant methods are ball-milling, spray-drying, melt-quenching and freeze-drying. This choice of polymer is expected to be an important formulation parameter.</td>
</tr>
</tbody>
</table>

**Supervisors:** Joint project with Thomas Rades and PhD student Jingwen Liu
**Research focus** lies in the development of solid oral dosage forms, including preformulation, formulation, processing and manufacturing together with the relevant solid-state characterization and quality control. This includes in particular the development of amorphous and co-amorphous systems as well as amorphous solid dispersions.

### Examples of projects

#### On the role of water in amorphous systems.

**On the role of water in amorphous systems.** Water is generally seen as detrimental for the stability of amorphous drugs and solid dispersions. However, initial in-house work has shown that this may not necessarily be true for all systems especially at low water concentrations. The aim of this Masters project is to determine the water absorption and stability of a range of amorphous systems (pure drugs, amorphous solid dispersions with polymers and co-amorphous systems with amino acids) in the presence of different amounts of water. The student will learn preparative techniques, including ball milling and quench cooling as well as using a wide range of analytical techniques, including X-ray powder diffraction, FTIR spectroscopy, thermal analytical techniques, water determination and dissolution techniques.

**Supervisors:** *Project in co-operation with Matthias Manne Knopp (suitable for 2 MPharm Students).*

#### Electrospun amorphous solid dispersions of poorly water-soluble drugs.

The development of oral dosage forms from poorly water-soluble active pharmaceutical ingredients (APIs) remains a major challenge for the pharmaceutical industry. Preparing amorphous solid dispersions (ASDs) allows increasing the solubility and dissolution rate of an API, hence, increasing its bioavailability. The application of electrical energy during electrospinning can generate ASD nanofibers from drug-loaded solutions and melts. This project focuses on the development of an electrospinning method to produce ASDs. The electrospun fibers will be comprehensively characterized by a range of analytical techniques, including scanning electron microscopy, X-ray powder diffraction, differential scanning calorimetry and dynamic mechanical analysis. The dissolution rate advantage will also be determined.

**Supervisors:** *Project in co-operation with Andrea Heinz (suitable for 2 MPharm Students).*
Korbinian Löbmann  
Associate Professor  
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**Research focus** lies in the development of solid oral dosage forms, including preformulation, formulation, processing and manufacturing together with the relevant solid state characterization and quality control. This includes in particular the development of new enabling formulation strategies, such as microwave amorphization (*in situ* amorphization) as well as novel excipients, such as mesoporous silica or deep eutectic solvents.

**Examples of projects**

**In situ amorphization using microwave irradiation**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Physically stable tablet during manufacturing and storage, as the drug is crystalline</td>
</tr>
<tr>
<td>2.</td>
<td>The tablet is microwave activated prior to administration, i.e. the drug forms a solid dispersion with a polymer and becomes amorphous</td>
</tr>
<tr>
<td>3.</td>
<td>Administration of the activated and highly soluble tablet</td>
</tr>
</tbody>
</table>

A major concern of amorphous formulations is their physical instability, which puts the gain in solubility at risk upon long time storage. Using microwaves, it is possible to transform a crystalline drug into its highly soluble amorphous counterpart within the final dosage form (tablet). Two projects are available and aim to develop new drug delivery systems that can be “activated” using microwaves.

**Supervisors: Projects in co-operation with PhD students Nele Hempel and Tobias Holm.**

**Development of novel DES based supersaturating drug delivery system for poorly soluble drugs**

Deep eutectic solvents (DESs) are mixtures of two organic compounds, such as amino acids, sugars or carboxylic acids, which in combination are liquid at room temperature. The solubility of drugs in DESs can be up to 55,000 fold higher than in water. Hence, DESs are a potential drug delivery system for poorly soluble drugs. The aim of this project is to identify feasible drug/DES combinations and develop a supersaturating drug delivery system capable of maintaining the drug in the supersaturated state.

**Supervisors: Project in co-operation with PhD student Henrik Palmelund (suitable for 2 Students).**

**Tiny medicine sponges – Understanding drug adsorption and molecular mobility in mesoporous silica**

Mesoporous silica (MS) is an excipient that can stabilize the amorphous form of a drug via surface adsorption in a monolayer. One project aims to increase the mechanistic understanding of molecular interactions and mobility of adsorbed drug monolayers on MS surfaces. A second project aims to increase the understanding of the monolayer mobility and phase transition, which we recently were able to experimentally identify.

**Supervisors: Project in co-operation with senior scientist Matthias Manne Knopp (Bioneer:Farma).**
12 Surface and Colloid Chemistry Group

https://pharmacy.ku.dk/research/surface-colloid-chemistry/

List of potential thesis supervisors:

**Martin Malmsten**
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13:305
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**Elisa Parra-Ortiz**
Assistant Professor
13:308A
Elisa.Parra@sund.ku.dk

Short description of research field:

The Surface and Colloid Chemistry Group focuses its research on physicochemical aspects of drug delivery, particularly for amphiphilic host defense peptides and nanoparticulate delivery systems. For these systems, we employ a range of surface and colloid chemistry techniques, including ATR-FTIR, QCM-D, SAXS, and light scattering. In addition, we have expanded our research to include neutron scattering, mainly neutron reflection but also SANS, e.g., for studies of the interactions of amphiphilic peptides and nanoparticulate delivery systems with model lipid membranes. Such physicochemical studies are matched with biological experiments so that key structural and dynamic issues determining the biological performance of systems can be elucidated.
Examples of projects

| Membrane interactions of structured silica nanoparticles as antimicrobial agents |
| In the wake of increasing bacterial resistance against conventional antibiotics, there is a growing interest in alternative approaches for reaching antimicrobial effects. Among those, nanoparticles are attracting considerable current interest due to the comparatively low cost, good scalability, and broad versatility of such materials, but also due to presently undeveloped bacterial resistance. Here, various nanomaterials offer opportunities for triggered functionalities to combat challenging infections. Although the performance in these diverse applications is governed by a complex interplay between the nanomaterial, the properties of included drugs (if any), and the biological system, nanoparticle-membrane interactions constitute a key initial step and play a key role for the subsequent biological response. Clarifying key factors controlling membrane binding and destabilization of nanoparticles is therefore key for the successful development of the latter towards therapeutics. In the present project, membrane interactions will be investigated for mesoporous silica nanoparticles, which offer opportunities in combating challenging infections. For example, both low molecular weight and biomacromolecular drugs can be readily incorporated into such nanoparticles, allowing large drug loads due to their large specific surface area. In addition, silica nanoparticles can be designed to display needle-like surfaces, which may be used to effectively “puncture” bacterial membranes by “needle-like” actions. Within the project, factors determining membrane interactions of “spiky” mesoporous silica nanoparticles will therefore be investigated by previously developed model lipid membranes, in combination with various biophysical techniques, such as QCM-D, ATR-IR, and light scattering. Results from such biophysical studies, e.g., on effects of membrane composition, structure and charge of the silica nanoparticles, and effects of co-administration of such particles with other potent antimicrobial agents, notably antimicrobial peptides, will be correlated to biological results on antimicrobial effects and cell toxicity for selected systems. |

**Supervisors:** Martin Malmsten & Elisa Parra-Ortiz
### Elisa Parra-Ortiz
**Assistant Professor**  
**13:308B**  
[Elisa.Parra@sund.ku.dk](mailto:Elisa.Parra@sund.ku.dk)

**Research focus:** Nanoparticle interactions with lipid membranes

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**Examples of projects**

<table>
<thead>
<tr>
<th><strong>Applications of oxidative stress on lipid membranes as a new tool for developing new antimicrobial agents</strong></th>
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<tbody>
<tr>
<td><strong>Aiming to improve the efficacy and safety of novel therapeutics and based on important advances in material science, drug delivery research is currently undergoing considerable growth to include a range of interesting nanomaterials. Particularly, inorganic nanoparticles are very attractive as antimicrobial agents (‘nanobiotics’), notably due to the increasing resistance development against conventional antibiotics. Apart from scalability and versatility, such materials offer advantages related to responsiveness of antimicrobial and anti-inflammatory effects and the possibility of controlling them by a range of triggering factors.</strong></td>
</tr>
<tr>
<td><strong>Generally, oxidative stress is known to be a key antimicrobial mechanism for a range of nanomaterials such as TiO₂ nanoparticles, which can be activated by UV light. However, studies on the mechanisms underlying this remain scarce. Based on previous work done by our group on the oxidative destabilization of lipid membranes, and using different biophysical and surface-chemical techniques, the present project will focus on the effects of nanoparticle-induced oxidative stress on lipid degradation, its consequences for membrane structure and stability, and any potential membrane selectivity that could allow more efficient antimicrobial activities along with reduced side effects. In a wider perspective, this project will contribute to the mechanistic foundation for the use of photocatalytic nanomaterials as antimicrobial agents.</strong></td>
</tr>
</tbody>
</table>

**Supervisors:** Elisa Parra-Ortiz & Martin Malmsten
13 Toxicology and Drug Metabolism

We perform experimental research revealing the occurrence, fate, and toxicological and endocrine effects of xenobiotics, especially pharmaceuticals, with the aim of assessing their risks to humans and biota. We apply various in vitro, ex vivo and in vivo assays and advanced analytical techniques, such as LC-MS and mass spectrometry imaging.

See website for Toxicology and Drug Metabolism Laboratory

Supervisors

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Please find examples of projects in Toxicology and Drug Metabolism Laboratory on the following pages.
**Main supervisor: Bjarne Stylishave**

**Endocrine disrupting pharmaceuticals:** Endocrine disrupting drugs (EDPs) are presumed to affect reproductive ability. EDPs are, however, generally much less potent than physiological hormones, and therefore there is doubt as to whether or not these substances can affect humans. Recent research indicates that simultaneous exposure to a cocktail of endocrine disrupting drugs, each at a concentration below the effect level, might result in additive or synergistic effects. The present project wishes to uncover interactions between selected hormone-disturbing substances in various *in vitro* test systems and/or animal experiments.

**Danida project: Green Resource Innovations for Livelihood Improvement**

Medicinal plants as green resource products (GRPs) are used as traditional medicine in Tanzania. Unfortunately, many herbal products are adulterated with drugs, such as antibiotics, antimalarials and mild analgesics. The present study aims to investigate the adulteration of herbal drugs from Tanzania, by analysing the presence of different drug classes in herbal medicines collected from markets and health providers in Tanzania. The project included approximately 3 months of field work in Tanzania.

**Azole transport in the human term placenta**

Azole drugs are highly efficient drugs against fungal infections. However, azoles are notoriously known for their endocrine effects. Since pregnant women are at increased risk of experiencing fungal infections, there is a growing concern that azoles will pass the placenta and exert endocrine effects on the developing fetus. In this project, we investigate the placental transport of azole fungicides widely used during pregnancy, and the ability of the placenta to regulate sex steroids during treatment to azole drugs.

**Pancreatic infections: Local and systemic antibiotics in infected walled-off pancreatic necrosis.**

Severe acute pancreatitis is characterized by organ dysfunction and necrosis of the pancreas. Mortality is high, up to 20%. After 3-4 weeks the necrosis becomes encapsulated a so-called walled-off necrosis (WON). The primary treatment is systemic antibiotics. However, little is known about the penetration of antibiotics into the necrosis and the ability of antibiotics to stop the infection. Using 2D-DESI-imaging and LCMS/MS, this project aims to investigate the distribution of the most commonly used antibiotics in pancreatic necrosis. The purpose is to identify the most effective treatment, thereby decreasing mortality and morbidity in patients suffering from pancreatic necrosis.
Main supervisor: Andreas Kretschmann

Development of a microfluidic assay for testing the endocrine disrupting potential of pharmaceuticals

Certain groups of drugs, such as azole fungicides, have enormous potential to disrupt the hormone system in humans and are suspected to contribute to the worldwide increasing incidence of birth defects, infertility, cancer and obesity. However, information on unintended effects of drugs on the human hormone system is in general scarce. One problem is that existing in vitro assays, which can measure the endocrine disrupting potency of drugs, are too time demanding and too expensive. The goal of this Master thesis is therefore the development of a microfluidic assay for the high throughput screening of drugs for their endocrine disrupting properties. Within this project an OECD standardized cell-based in vitro assay (H295R steroidogenesis assay), which can detect effects of drugs on the steroid hormone system, will be miniaturized on a microchip. The microassay will be validated with azole antifungal drugs, which are known to inhibit the synthesis of hormones like the sex steroids testosterone and estradiol.

**Supervisors: Andreas Kretschmann, Joerg P. Kutter. No. of students: 1-2**

Endocrine toxicity of drug enantiomers and metabolites

Increasing evidence exists that certain pharmaceuticals disturb the human hormone system and may contribute to endocrine related diseases like infertility, obesity and different types of cancers. It is well known that enantiomers of drugs can differ strongly in their biological activity. Furthermore, drug metabolites formed in the body can be active and possess higher activity than the parent compound. Very little is known about how the endocrine disrupting potency of a drug depends on its enantiomeric form and its metabolic products.

The focus of this project are chiral drugs like azole fungicides, which are used for the treatment of severe systemic and superficial fungal infections. The goal of this project is to elucidate the endocrine toxicity of azole enantiomers and metabolites through pharmacokinetic and –dynamic studies. The practical work includes enzyme and cell based in vitro assays as well as in vivo experiments. A large part of the project is the development of analytical chemical methods for the identification and quantification of enantiomers and metabolites in different biological matrices with enantioselective HPLC-MS/MS.

**Supervisors: Andreas Kretschmann, Bjarne Styrishtave, Claus Cornett. No. of students: 1**
**Christian Janfelt**  
Associate professor  
Building 18, 3rd floor, 18.3.306  
christian.janfelt@sund.ku.dk

**Research focus:** Development and application of **Mass spectrometry imaging (MSI)** in drug delivery, pharmacology, medical diagnostics and natural products. MSI makes it possible to image the distribution of drug and endogenous compounds on surfaces. In this way, we can for example follow a drug dosed to an animal to see where the drug goes and how it is metabolized, where a tumor is localized or where in a plant different natural products are synthesized. The information can be combined in colored images to show e.g. if a drug reaches the tumor which should be treated and which impact different drug delivery technologies have on delivery of drug through e.g. skin, intestine or in lungs.

**Examples of projects**

**Mass spectrometry imaging of drugs in tissue sections from mice**

In this project, a mouse will be dosed with a drug, and subsequently the whole mouse or single organs (brain, liver and kidney) will be cut in thin slices, which are then analysed with DESI-MSI. The aim of the project is to image where the drug goes and in which doses we can see the drug and its metabolites. The project will be planned in collaboration with pharmacologists or medicinal chemists.

**High-resolution MALDI mass spectrometry imaging for studies in drug delivery**

A new laser-based mass spectrometry imaging setup has been installed, which enables mass spectrometry imaging at the cellular level. The delivery of drugs across biological membranes and barriers will be studied in ex-vivo and possibly in-vivo animal experiments. High-resolution mass spectrometry images showing the distributions of drugs and other exogenous compounds relative to endogenous compounds (e.g. membrane lipids) will provide information about the efficacy and mechanism of new drug formulations. The project will be in collaboration with one of the Drug Delivery groups at the Dept. of Pharmacy.

**Mass spectrometry imaging in cancer research and in development of skin cancer treatment**

The capabilities of DESI-MSI and MALDI-MSI to image the distribution of endogenous compounds together with a drug and its metabolites make them ideal in the study of cancer treatment by chemotherapy. Biomarkers of the tumor can be identified and the drug delivery can be imaged relative to the tumor tissue. In this project MALDI imaging and LC-MS will be used to optimize the delivery of one or more chemotherapy agents by imaging of tissue sections from difference depths in the treated skin. The study will be carried out in healthy pig skin, a mouse model of skin cancer or in clinical samples from cancer surgery. This project takes place in collaboration with Department of Dermatology, Bispebjerg Hospital, which develops new treatments for skin cancer.
14 Vaccine Design and Delivery

https://pharmacy.ku.dk/research/vaccine-design-delivery/

List of potential thesis supervisors:

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13.7.714  
camilla.foged@sund.ku.dk

Aneesh Thakur  
Postdoc  
13.7.712  
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Short description of research field:

The research focus of the Vaccine Design and Delivery Group is advanced drug delivery. The group uses *in vivo* imaging (e.g., NIR, MRI and SPECT/CT) to guide and optimize the design of new nanoparticle-based delivery systems for vaccines and nucleic acid-based therapeutics to improve therapy. The research in the group is highly interdisciplinary. The team comprises international researchers of various backgrounds, including pharmacists, biologists, biochemists, physicists and biotechnologists.

“Biopharmaceuticals like vaccines and nucleic acid-based therapeutics are challenging from a pharmaceutical perspective, because they are highly complex products, which can only be understood via solid fundamental science. Using systematic knowledge-based quality-by-design approaches, combined with advanced physicochemical and biopharmaceutical assessment, and molecular imaging, we design new delivery systems for biopharmaceuticals to optimize their stability, efficacy and safety” says Professor and Group Leader, Camilla Foged.

The overall research goal is to improve disease prevention and treatment in the fields of infectious and inflammatory diseases, and cancer. The group is addressing drug delivery challenges from bench-to-bedside, via international collaborations, using state-of-the-art technologies. This has fostered innovative solutions and high-impact publications in drug delivery.
Research focus: One of the primary goals of the Vaccine Design and Delivery Group is to gain new fundamental knowledge that can facilitate the design, optimization and development of novel delivery systems capable of delivering loaded biopharmaceuticals to the intended target site(s). The Vaccine Design and Delivery Group addresses the complex challenges associated with the formulation and targeted delivery of vaccines and nucleic acid-based therapeutics.

Examples of projects

Microfluidics-assisted design of next-generation mRNA vaccines - a novel tool for fighting cancers and challenging infectious diseases

There is an unmet medical need to develop novel vaccines against the so-called “difficult targets” such as AIDS, TB and cancer. One promising strategy is the use of vaccines based on mRNA that encode antigenic proteins from pathogens or tumor cells. Using microfluidics, we will develop multifunctional nanoparticle-based vaccine that both delivers mRNA encoding antigen and induces CTL responses. The efficacy and safety of the mRNA vaccines will be tested in animal models of infection and cancer.

Supervisors: Aneesh Thakur

Magnetic resonance imaging-assisted design of a thermostable and self-administrable tuberculosis vaccine for inhalation

Tuberculosis (TB) is caused by Mycobacterium tuberculosis, which enters the lungs through the respiratory mucosa. The objectives of the project is to develop a dry powder-based vaccine against TB and using MR imaging, to define the specific areas in the lungs, which are optimal for vaccine deposition, efficacy and safety. Using a benchtop aerosol generator, PreciseInhale, we will deliver the dry powder liposome-adjuvanted vaccine formulation in mice lungs and evaluate the safety and pulmonary distribution using mass spectrometry imaging. The immunogenicity and efficacy of the dry powder vaccine will be tested in animal models of Tuberculosis challenge.

Supervisors: Aneesh Thakur

Design and investigation of nanoparticles for targeted delivery of small interfering RNA (siRNA)

Small interfering RNA (siRNA) holds a promising therapeutic potential for treating a variety of diseases via gene silencing. However, the physicochemical properties of siRNA often limit its therapeutic efficacy rendering it unfavourable for efficient intracellular delivery. We have developed lipidoid-polymer hybrid nanoparticles (LPNs) and demonstrated safe and efficient intracellular delivery of siRNA. In this project, new generation of lipidoid-based LPNs will be evaluated for their transfection efficiency, safety, and therapeutic effect in animal models of acute inflammation.

Supervisors: Aneesh Thakur