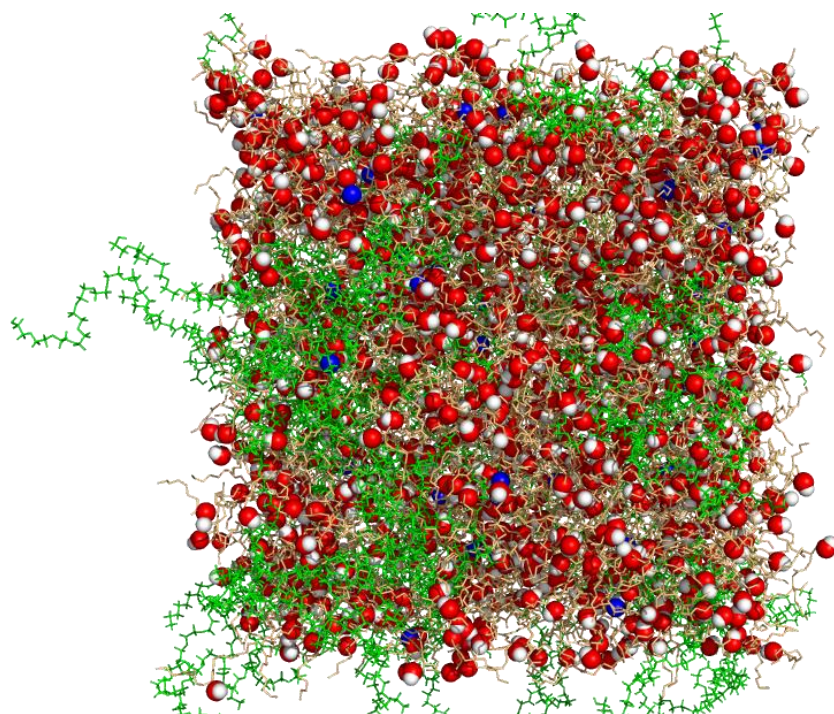


Department of Pharmacy

ANNUAL REPORT 2015



Department of Pharmacy

**ANNUAL REPORT
2015**

Preface

Welcome to the Annual Report of the Department of Pharmacy at Uppsala University. Apart from the Chairman's report, the report contains brief summaries of current research, as well as publication lists. More information about the department, our research, and other activities can be found at our web page, <http://www.farmfak.uu.se/farm/>.

I would like to express my sincere thanks to all personnel and students at the Department for their dedication and hard work during the year. I would also like to thank all the organizations and companies contributing to our research and teaching, either by participation in our research and teaching activities, or through provision of funding. I look forward to further fruitful collaboration during the coming year.

Uppsala 2016-04-03

A handwritten signature in black ink, appearing to read 'Martin Malmsten', with a long horizontal flourish extending to the right.

Martin Malmsten

Chairman, Department of Pharmacy

List of Contents

Chairman's report	5
Research	7
PhD education	7
Undergraduate education	8
Collaboration with society	9
Personnel	9
Administration and economy	9
Organization and personnel	11
Scientific reports	27
Biopharmaceutics	29
Drug Delivery	38
Pharmacy Practice and Policy	55
Pharmaceutical Physical Chemistry	58
Pharmaceutics	69
Pharmacoepidemiology and Pharmacoeconomics	78
Other information	82
Dissertations	83
Awards	84
Fellowships	85
Addresses	86

Chairman's report

Research

The research performed at the department is centered around three different aspects of pharmaceuticals, i.e.,

1. Drug optimization
2. Drug delivery and pharmaceutical formulation
3. Rational drug usage

Within this overall frame, research is performed by our six research groups:

- *Biopharmaceutics* studies the interaction between drugs and biological processes, e.g., membrane transport and metabolism, and develops new concept formulations for drug delivery.
- *Drug Delivery* studies absorption, distribution, transport, and metabolism, as well as drug delivery, and develops new in vitro and computer models for predictions of ADMET properties of drugs.
- *Pharmacy Practice and Policy* focuses on societal aspects of pharmaceuticals and pharmacists, e.g., patient safety, the role of pharmacists, and communication issues related to the use of drugs.
- *Pharmaceutical Physical Chemistry* develops design principles for pharmaceutically relevant systems at a molecular and colloidal scale.
- *Pharmaceutics* studies pharmaceutical formulation and manufacturing.
- *Pharmacoepidemiology and Pharmacoeconomics* studies the causes and effects (clinical as well as social and economic) of the use of pharmaceuticals from a population perspective.

More information about our research follows in the reports of the groups below.

PhD education

With a continued demand for pharmaceutically oriented PhDs in academic, industrial, regulatory, and pharmacy sectors, the department maintains a high ambition regarding PhD education. The work of our PhD students contribute critically to both research and teaching at the department. The career paths for our PhDs remains both within and outside academia, e.g., within pharmaceutical industry, pharmacies, and agencies. This is an indication of the appreciation of our PhD training from society at large. Although the pharmaceutical sector in Sweden is under substantial changes, our PhDs have been able to find qualified positions after graduation.

Undergraduate education

The Pharmacy discipline is broad, with interfaces to science, technology, and social studies. Considering this, our teaching program is broad, and includes a number of subjects. To run the teaching program, our staff is organized in four teaching groups, each group supported by a director of studies. The groups are related to the main disciplines taught, i.e.,

1. Pharmaceutical physical chemistry
2. Pharmaceutics and biopharmaceutics
3. Social pharmacy
4. Pharmacoepidemiology

The department is currently involved in teaching at six education programs, i.e.,

1. Master in Pharmacy, Uppsala University
2. Bachelor in Pharmacy, Uppsala University
3. Master in Chemical Engineering, Uppsala University (with possibility to specialize in pharmaceutical sciences)
4. Master in Biomedicine, Uppsala University
5. Master in Drug Development, Uppsala University
6. Master in Drug Usage, Uppsala University

By tradition, the major parts of the undergraduate teaching at the department are within the two Pharmacy programmes, i.e., Master in Pharmacy and Bachelor in Pharmacy, at Uppsala University.

Within the programs, courses are given on basic and advanced levels. On the basic level, the courses are of broad content, covering the breadth of the discipline and with a course content that compares with international curriculum on this level. The advanced level consists of courses intended to give depth on certain selected subjects. The subjects dealt with are related to on-going research projects at the department and thus corresponds to the specific expertise of our staff. In all our disciplines we also offer Bachelor and Master theses courses as a means for the student specialization on a Pharmacy discipline.

It should be mentioned, finally, that the department has a long tradition of regularly giving courses intended for professionals in the form of commissioned teaching to agencies and industrial and other professional organizations.

In total, the department teaches around 40 different courses each year at different levels and with students of different backgrounds. The teaching program is thus both extensive and complex and requires a relatively large number of staff of broad knowledge.

During 2015, considerable activities have been devoted to developing the Master in Pharmacy programme. The work has involved the entire Faculty of Pharmacy, as well as input from our Advisory Group and other stakeholders. While we have still not completed this process, it is rewarding to notice the enthusiasm and commitment the new programmes generate.

Collaboration with society

Many of our researchers and teachers are involved in collaboration with society in different ways. Besides the responsibility of scientists to communicate with the public through newspapers, radio, TV, etc., the collaboration with society today include a broad range of activities, including expert commissions to agencies and scientific societies, as well as innovation and commercialization activities. It is worth noting in this context that several pharmaceutical companies – about 10 companies over the years - have emerged from research conducted in our department. Relevant examples of such activities can be found in the list of commitments of staff later in this document.

Personnel

During 2015, personnel situation at the department has been relatively stable from a personnel turnover perspective, although increased focus on larger research programs from both national and international funding agencies necessities larger flexibility in our organization, which is reflected also in an increase in specified time employments, not the least as researchers. With our spread of research and teaching activities, finding good personell is key. We are therefore happy to report that during the year, this has worked well.

Administration and economy

The regular university funding for research to the department has been relatively stable over the last few years. Combined with relatively strong external research funding, and balanced capital, the economic situation regarding research activities is stable, and has during 2015 allowed for continued investments in strategic research developments. The varying funding for the undergraduate teaching does, however, remain a problem for the department, as well as for the Faculty of Pharmacy. Actions to address this have therefore been launched during the year.

Revenues to the Department of Pharmacy 2015 (kSEK)

University funding - Undergraduate teaching	18 424
Contract teaching	759
University funding - Research and post-graduate teaching	28 573
Research grants	22 538
Commissioned research	<u>1 653</u>
Total	71 947

Organization and personnel

Organization

Chairman

Martin Malmsten

Deputy chairman

Erik Björk

Department board

Martin Malmsten, chairman

Göran Alderborn, teacher representative

Per Hansson, teacher representative

Erik Björk, teacher representative, deputy

Christin Magnusson, teacher representative (Jan-Jun)

Christel Bergström, teacher representative

Göran Frenning, teacher representative (Jul-Dec), deputy (Jan-Jun)

Johan Gråsjö, representative for technical/administrative personnel, deputy

Richard Svensson, representative for technical/administrative personnel

Elsa Lilienberg, graduate student representative

Linda Alskär, graduate student representative

Lina Nyström, graduate student representative, deputy

Kia Ropponen, student representative (Jan-Jun)

Maram Zaya, student representative (Jul-Dec)

Eva Nises Ahlgren, secretary (Jan-Feb)

Heléne Lyngå, secretary (Mar-Dec)

Director of graduate studies

Göran Frenning

Directors of undergraduate studies

Charlotta Alvarmo

Jonas Gernandt (Jan-Jun)/Magnus Bergström (Jul-Dec)

Kerstin Bingefors

Christin Magnusson (Jan-Jun)/Erik Björk (Jul-Dec)

Computers and web

Göran Ocklind

Personnel

Senior staff

Bertil Abrahamsson, PhD, Adjunct professor
Göran Alderborn, PhD, Professor in Pharmaceutical Technology
Charlotta Alvarmo, Lecturer
Per Artursson, PhD, Professor in Dosage Form Design
Christel Bergström, PhD, Associate professor
Magnus Bergström, Senior lecturer
Kerstin Bingenfors, PhD, Senior lecturer
Erik Björk, PhD, Senior lecturer
Göran Frenning, PhD, Professor in Pharmaceutical Physics
Jonas Gernandt, PhD, Senior lecturer
Per Hansson, PhD, Professor in Physical Chemistry
Dag Isacson, PhD, Professor in Pharmacoepidemiology
Hans Lennernäs, PhD, Professor in Biopharmaceutics
Jonas Lundkvist, PhD, Associate professor
Christin Magnusson, BSc, Lecturer
Denny Mahlin, PhD, Associate professor
Martin Malmsten, PhD, Professor in Pharmaceutical Physical Chemistry
Pär Matsson, PhD, Assistant professor
Josefina Nordström, Senior lecturer
Erik Sjögren, PhD, Senior lecturer
Jannike Stenlund, MSc, Lecturer
Helena Wennborg, MD PhD, Guest lecturer
Katarina Öjefors-Stark, PhD, Lecturer

PhD Students

Emelie Ahnfelt
Linda Alskär
Caroline Alvebratt
Sara Andersson
David Dahlgren

Supervisors

Hans Lennernäs
Christel Bergström
Christel Bergström
Christel Bergström
Hans Lennernäs

Ilse Dubbelboer	Hans Lennernäs
Khadijah Eudeng	Christel Bergström
Johanna Eriksson	Hans Lennernäs
Niklas Handin	Per Artursson
Mina Heidarian Höckerfelt	Göran Alderborn
Joel Hellrup	Denny Mahlin
Claes Jidheden	Per Hansson
Henrik Jonsson	Göran Frenning
Elsa Lilienberg	Hans Lennernäs
Sara Malekkhaiat Häffner	Martin Malmsten
André Mateus	Per Artursson
Randi Nordström	Martin Malmsten
Lina Nyström	Martin Malmsten
Samaneh Pazesh	Göran Alderborn
Carl Roos	Hans Lennernäs
Jonas Rudén	Göran Alderborn
Shalini Singh	Martin Malmsten
Andrea Treyer	Per Artursson
Christine Wegler	Per Artursson
Ronja Widenbring	Martin Malmsten
Kristin Wisell	Sofia Kälve mark Sporrang
Magnus Ölander	Per Artursson

PhD Student, external

Supervisor

Pia Frisk	Sofia Kälve mark Sporrang
Lena Thunander Sundbom	Kerstin Bingefors

Research scientists

Amjad Alhalaweh, PhD
 Maria Backlund, PhD
 Pawel Baranczewski, PhD
 Kathryn Browning, PhD
 Yanling Cai, PhD

Stefano Colombo, PhD
Jonas Fagerberg, PhD
Fabienne Gaugaz, PhD
Michael Holmboe, PhD
Georgiy Khodus, PhD
Per Larsson, PhD
Maria Karlgren, PhD
Lucia Lazorova, PhD
Patrik Lundquist, PhD
Josefina Nordström, PhD
Ann-Sofie Persson, PhD
Aljona Saleh, PhD
Ivailo Simoff, PhD
Erik Sjögren, PhD
Richard Svensson, PhD
Ursula Thormann, PhD

Administrative and technical staff

Johan Gråsjö, PhD
Pernilla Larsson
Karin Johansson
Maria Mastej, BSc
Eva Nises Ahlgren, BSc
Göran Ocklind, PhD
Elin Khan, MPharm
Annette Svensson Lindgren
Lise-Britt Wahlberg
Ulla Wästberg Galik
Heléne Lyngå
Emma Homberg
Caitlin McEvoy

Mini-biographies of permanent staff (January 1st 2016)

Alderborn, G.

Research interests

Göran Alderborns research centers on particle science and formulation technology for pharmaceutical products. Current research projects focus on the characterization of mechanical properties of powders, the engineering of granular materials and process induced amorphisation of particles.

Examples of current commitments

- Dean of the Faculty of Pharmacy, Uppsala University
- Coordinator research infrastructure at the scientific domain of medicine and pharmacy, Uppsala University
- Member of the Editorial Board of Int J Pharm
- Member of the Editorial Advisory Board of Pharm Dev Technol
- Member of the Swedish Pharmacopoeia Commission, Medical Products Agency, Uppsala
- Member of the Powder Working Party of the European Directorate for the Quality of Medicines
- Member of the Board of the IF Foundation for Pharmaceutical Research, Stockholm

Artursson, P.

Research interests

Current research interests are directed towards predictive pharmacokinetics (ADMET) and biopharmaceutics in drug discovery and development. In particular, the role of drug transporting proteins for the cellular uptake, target engagement, metabolism and elimination of drugs and drug-like molecules is studied.

Examples of current commitments

- Director for the ADMET facility within the Drug Discovery and Development Platform at the Science for Life Laboratories
- Facility Director at the Chemical Biology Consortium Sweden
- Member of the Scientific Advisory Board of the Medical Products Agency
- Member of the Board of Governors of Globalization of Pharmaceutics Education Network Inc. (GPEN)

- Member of the Editorial Board of Pharm Res
- Member of the Editorial Board of J Pharm Sci
- Member of the Editorial Board of Eur J Pharm Sci
- Member of the Editorial board of The Scientific World Journal
- Member of the Editorial Board of Current Drug Delivery
- Review editor of Frontiers in Drug Metabolism and Transport
- Honorary Professor at the University of Queensland, Brisbane, Australia

Baranczewski, P.

Research interests

Current research interests are directed towards development of in vitro ADME methodology, in vitro-in vivo extrapolation (IVIVE) and predictive pharmacokinetics (PBPK) in drug discovery and development. In particular, the use of proteomics approaches for quantification of ADME proteins in cell systems and human tissues is under development. This knowledge will be used for improvement of IVIVE and PBPK models, and also for development of new model(s) for prediction of drug delivery and thus target efficacy.

Examples of current commitments

- Facility manager, UDOPP
- Member of Portfolio Management Committee at the European Gram Negative Antibacterial Engine (ENABLE) consortium within the New Drugs for Bad Bugs (ND4BB) Innovative Medicine Initiative (IMI) program.
- Member of Project Implementation Committee at the European Gram Negative Antibacterial Engine (ENABLE) consortium within the New Drugs for Bad Bugs (ND4BB) Innovative Medicine Initiative (IMI) program.

Bergström, C.

Research interests

Research is performed in the interface between medicinal chemistry, physical chemistry, pharmaceuticals and biopharmaceuticals. Experimental methodologies are combined with computational tools to interpret, understand and predict properties related to drug formulation, dissolution, solubility and absorption. Focus is set on the development of rapid and accurate models, experimental as well as computational, to allow assessment of the potential for a drug candidate to be developed into a well functioning drug as early as possible in the drug discovery and development process.

Appointments

Adjunct Associate Professor, Monash University, Oct 2012-present.

Examples of current commitments

- Adjunct Associate Professor at Monash Institute of Pharmaceutical Sciences, Monash University
- Member of the Board of the Controlled Release Society Nordic Chapter
- Member of the PhysChem Forum committee
- Member of organizing committee for conferences and courses, exemplified by CRS Nordic Chapter summer school 2013.

Bingefors, K.

Research interests

Chris Bingefors works in the field of pharmacoepidemiology and pharmacoeconomics. Main research areas are public health, quality of life and health services research with a special emphasis on the use of drugs. Her particular interests are psychiatric problems, pain and dermatology. Another area of expertise is the use of drugs from a gender perspective.

Examples of current commitments

- Co-editor, Value in Health
- Member of the editorial board, International Journal of Pharmacy Practice
- Member of the core curriculum group: The Philosophy of Life and Modern Society. Centre for Environmental and Development Studies (CEMUS), Uppsala University
- Director of undergraduate studies in pharmacoepidemiology and pharmacoeconomics

Björk, E.

Research interests

Erik Björk's research focuses on mucosal transport of drugs, especially formulation aspects. Specific interest is nasal systemic transport, olfactory transport and transdermal administration of drugs.

Examples of current commitments

- Member of the board of Section for Pharmaceutics and Biopharmaceutics. The

Frenning, G.

Research interests

Göran Frenning's research aims at enhancing the understanding of pharmaceutical processes through mechanistic modelling. His work is mainly directed towards particle-scale modelling of powder processes such as powder compression/compaction and powder flow, but also encompasses modelling of drug release, for example the release of cationic mixtures from gels. Experimental work aiming at evaluating the developed models is an important part of these efforts.

Examples of current commitments

- Deputy member of the Committee for postgraduate studies at the Faculties of Medicine and Pharmacy
- Director of graduate studies at the Department of Pharmacy
- Member of the Gender Equality Committee at the Department of Pharmacy

Gaugaz, F.

Research interests

Fabienne Gaugaz is interested in the development of specific and selective treatments for cancer and in determining the efficacy of such drug candidates. Current research focuses on the targeted proteomic analysis of drug transporters, drug metabolizing enzymes and drug targets in healthy and cancerous tissue as components of a target efficacy model.

Hansson, P.

Research interests

Fundamental aspects of the interaction between charged polymers, in particular polymer networks, and oppositely charged macroions and amphiphilic self-assemblies in aqueous systems. Current focus is on the interaction of proteins and amphiphilic drugs with charged microgel networks and its implications on microgels as carriers of protein drugs and mechanisms of protein sorting. Of special interest are self-assembling properties and the interplay between electrostatic, excluded-volume, and elastic interactions in relation to phase transitions and molecular transport.

Examples of current commitments

- Member of the Committee of Education at the Faculty of Pharmacy, Uppsala University
- Chairman of the organizing committee of “Colloids and surfaces in biology and biomaterials”, a symposium on surface on materials chemistry in Uppsala in November 2015.

Isacson, D.

Research interests

Dag Isacson works in the field of pharmacoepidemiology and pharmacoeconomics. Main research areas are reasons for and consequences of the use of drugs from a population perspective. In the research adverse drug reactions, drug-related problems as well as adherence are studied. Of special interest is the relationship between use of drugs and quality of life. In this research different methods to measure quality of life (Rating Scale, Time Trade Off, EQ-5D and Health Related Quality of Life) are compared. Another area is the application of pharmacoepidemiology and health economics in pharmacy practice.

Karlgren, M.

Research interests

Maria Karlgren works in the area of ADME and predictive pharmacokinetics. More specifically, her research is focused on predictive cellular *in vitro* models for studying drug transport, drug-drug interactions, transporter pharmacogenomics and the interplay between drug transport and drug metabolism processes.

Examples of current commitments

- Member of the organizing committee of the Symposium on Pharmaceutical Profiling arranged by the Department of Pharmacy every second year
- Scientific advisor in molecular biology and *in vitro* drug transport, Uppsala University Drug Optimization and Pharmaceutical Profiling Platform (UDOPP)

Lennernäs, H.

Research interests

His research aims to develop novel strategies of tissue drug targeting and delivery that aims to improve the clinical use and efficacy of drugs in various disease states, such as metabolic, endocrinological and cancer diseases. Especially the use of formulation technologies to construct novel medical treatments is a major focus. His research interest is also focused on clinical significance of mechanisms and function of membrane transport and metabolism of drugs/metabolites in the gastrointestinal tract,

hepatobiliary system and cancer tissues. This work is performed in vivo with clinical models in humans and in various tissue and cell culture models. Hans Lennernäs has together with gastroenterologists developed and validated two new clinical intestinal perfusion techniques for investigations of intestinal transport and metabolism of drugs and nutrients. He is also one of the founders of the well-established Biopharmaceutics classification system. He has discovered and developed several pharmaceutical products based on drug delivery principles. The primary focus on the research is tumor drug delivery and new concepts for treatment of metabolic/endocrinological diseases.

Examples of current commitments

- Member of the board Uppsala Clinical Reserach Center (UCR), Uppsala University
- Member of the editorial board of Molecular Pharmaceutics
- Member of the editorial board of Therapeutic Delivery
- Member of the editorial board of Eur J Pharm Sci
- Member of the editorial board of BMC Pharmacology
- Member of the board of the Oral Drug Delivery Foundation, USA (a non-profit organisation for promotion of education and research)
- Member of the board of LIDDS AB (www.liddspharma.com)
- Member of the board of Empros Pharma AB, Solna
- Member of the board of Nanologica AB, Södertälje
- Member of the board of Recipharm Pharmaceutical and Manufacturing AB (www.recipharm.com)
- Member of the Executive Committee of OrBiTo (an IMI project) (www.liddspharma.com)
- Managing Entitiy for an IMI project (OrBiTo) (<http://www.imi.europa.eu/content/orbito>)

Lundquist, P.

Research interests

Patrik Lundquist works in the field of ADME where he has studied the interplay of drug metabolizing enzymes and transporters in drug disposition. He also has a long standing interest in epithelial transport processes. He currently focuses on the role of the intestinal epithelium as a barrier to the absorption of drug molecules and the possibility to use nanoparticles to increase the bioavailability of peptide-based drugs.

Mahlin, D.

Research interests

In his research, Denny Mahlin focuses on the solid-state structure and particle properties of drugs and pharmaceutical excipients. Of special interest is to understand the relations between the molecular/nano-scale properties and the functional properties of materials, such as physical stability, dissolution, powder flow and compactability. In particular the possibilities to utilize the amorphous form of excipients and active drug compounds, as well as the structure and dynamics of components in amorphous nano-composites are studied. Spray-drying and solid-state characterization techniques are central methods in the work.

Examples of current commitments

- Scientific Advisor to the Editors of JPharmSci
- Member of the Committee of Education at the Faculty of Pharmacy, Uppsala University
- Member of the Board of the Alumnföreningen Farmis, Faculty of Pharmacy, Uppsala University

Malmsten, M.

Research interests

Martin Malmsten's research focuses on the use of lipid and polymer systems as efficient discovery and delivery tools for bio-macromolecular drugs, notably antimicrobial and host-defense peptides. The research is focused on establishing an improved mechanistic understanding on the interaction between such drugs with complex lipid/cell membranes, as well as with nanoparticle drug delivery systems, and is based on extensive international research collaborations and state-of-the-art physicochemical methodologies.

Examples of current commitments

- Chairman of the Board of the Department of Pharmacy, Uppsala University
- Member of the Advisory Board of Bio-X
- Editor-in-Chief for the Journal of Colloid and Interface Science
- Section editor for Current Opinion of Colloid and Interface Science
- Member of the Editorial Board of Colloid and Interface Science Communications
- Member of the Editorial Board of the Encyclopedia of Surface and Colloid Science
- Guest professor Charité, Berlin
- Member of the Royal Swedish Academy of Engineering Sciences (IVA)

Matsson, P.

Research interests

Pär Matsson's research aims to determine the properties of small molecules that allow their development into successful therapeutics, with particular emphasis on how drug transport and metabolism pathways influence cellular drug exposure and effect. Current research involves a combination of experimental and computational techniques, including measurements of *in vitro* intracellular drug exposure, ligand and target based modeling of membrane transporters and drug-metabolizing enzymes, and chemical network modeling.

Examples of current commitments

- Chairman of the SciLifeLab The Svedberg seminar series at Uppsala University Biomedical Center
- Scientific advisor in computational chemistry, Uppsala University Drug Optimization and Pharmaceutical Profiling Platform (UDOPP)
- Member of the Board of the IF Foundation for Pharmaceutical Research, Stockholm
- Member of the International Transporter Consortium

Scientific reports

Biopharmaceutics

Professor Hans Lennernäs

The overall aim of this research program is to develop novel principles for an optimised drug delivery and targeting to diseased organ. The long-term goal is to improve pharmacological effect and therapeutic outcome by reaching the active site and/or specific organ(s) with high drug concentration at the right time and amount and consequently reduce unnecessary body exposure and adverse effects. The objective is to develop novel treatment principles with an improved benefit:risk ratio. In all cases the ongoing projects are driven by an obvious clinical need. Multi-disciplinary collaborations, using mainly clinical models, include research teams from pharmaceutical technology, material science, biopharmaceutics and pharmacokinetics, drug metabolism, toxicology, oncology, gastroenterology, endocrinology, urology and regulatory science. Projects are based on an in-depth understanding of the clinical significance and functional activity such as passive and carrier-mediated membrane transport processes and intracellular enzymatic processes. The disease-oriented projects have their targets in the intestinal-hepatobiliary systems, various tumour tissues and other target organs. Local modified release drug therapy is a particular strong focus in the future individualization of oncology treatments based on image guided techniques. Another strong research effort is to understand in the in vivo mechanisms determining gastrointestinal drug absorption, liver first-pass effect and biliary excretion. These findings are applied into discovery and development of novel oral drug delivery strategies.

The current research program has four projects:

- The ORBITO project aims to enhance the understanding of gastrointestinal absorption drugs from various pharmaceutical formulations, and apply this knowledge to create new experimental methods and theoretical models that will better predict the performance of these drugs in patients.
- Increase the understanding of novel oral formulations for poorly soluble compounds.
- Novel drug delivery approaches for drug targeting and local modified release of anti-cancer drugs based on pharmacokinetic, pharmacodynamic and clinical principles.
- Specific targeting to the hepatobiliary system based on ADME and clinical principles. Pharmaceutical development of novel treatments for liver cancer taking the role of local disposition in a diseased tissue into account. Building physiological based pharmacokinetic modelling with application to predicting and understanding the local disposition of drugs in liver cancer tissue and as well gastrointestinal drug absorption.

We are using advanced clinical research models (both in vivo and in vitro), which are well established in our laboratory (such GI-intubation techniques and Ussing chamber) to examine the complex in vivo intestinal absorption and entero-hepatobiliary handling

of drugs and metabolites in humans, with focus on transit, solubility-dissolution, membrane transport, metabolism and physiology. This research is a part of the ORBITO project. This research has also the potential to establish new in vivo valid principles for delivery and targeting of drugs to this enterohepatic cycle and to develop novel formulation principles for poorly soluble drugs. In addition, this project has the objective to better understand hepatobiliary kinetics and exposure of drug and metabolites in relation to toxicity issues. The oral drug delivery principles are also adjusted to normal physiology to be able to apply to circadian rhythms such as hydrocortisone replacement therapy in adrenal insufficiency. In addition, the biopharmaceutic research group is developing novel anti-cancer treatment approaches at various stages of development, providing exciting perspectives for the future of controlled release focal cancer cure. One important factor for a successful outcome of such therapeutic approaches is ensuring local specific targeting of the therapeutic moiety at the tumour site. In collaboration with clinical groups an increased understanding of the limitations of current therapies for liver cancer is the major objective. Based on this knowledge novel approaches for a more efficient and safe local chemotherapy is developed.

Professor Lennernäs is the inventor of more than 17 patents and patent applications. He is one of the innovators and developers of a novel sublingual drug delivery system currently used for the treatment of various acute pain conditions. He has also together with co-inventors initiated three start-up companies that has developed a novel oral replacement modified release product (approved by EMA in 2010) (www.duocort.com) for Addison disease, the innovation and development of local drug treatment of localised prostate and liver cancer as well as novel oral treatments for metabolic/endocrinological diseases (Empros Pharma AB).

Project members and collaboration partners

Projects 1 and 2: Biopharmaceutics and pharmacokinetics principles of oral drug delivery

Prof Hans Lennernäs, Prof Bertil Abrahamsson, Dr Erik Sjögren, David Dahlgren, Carl Roos, Prof. Per Hellström (MD) and collaborators Uppsala University hospital, University of Mainz, University of Michigan and National Veterinary Institute. Internal collaborators are Prof Martin Malmsten, Prof. Per Hansson, Prof Göran Frenning and Prof Göran Alderborn

Projects 3 and 4: Novel drug delivery approaches for drug targeting and focal controlled release of anti-cancer drugs

Prof Hans Lennernäs, Elsa Lilienberg, Ilse Dubbelboer, Emelie Ahnfelt, Dr Erik Sjögren, Prof. Rickard Nyman (MD), Dr. Charlotte Ebeling Barbier(MD). Prof. Per Stål (MD) and collaborators at Uppsala University hospital, Karolinska University hospital, Tampere University Hospital, Helsinki University hospital, and National Veterinary Institute

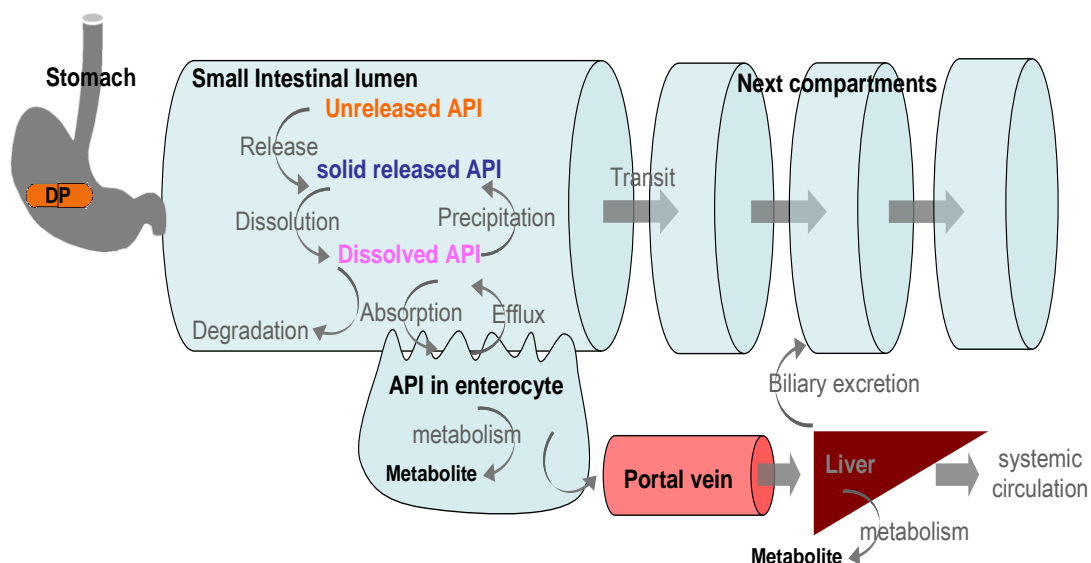


Figure 1. OrBiTo is new European project within the IMI programme in the area oral biopharmaceutics tool that include nine universities, one regulatory agency, one non-profit research organisation, three SMEs together with the twelve pharmaceutical companies (<http://www.imi.europa.eu/content/orbito>). The OrBiTo project will deliver novel methods and a framework for rational application of predictive biopharmaceutics tools for oral drug delivery. Biopharmaceutical parameters that are of main concern for a successful oral delivery include physical, chemical, and biological properties of the API, design and composition of the pharmaceutical formulation and the absorption conditions at different physiologically sites along the gastrointestinal (GI) tract. For instance, the transepithelial permeability changes to various extent along the small and large intestine for drugs transported by passive diffusion and/or carrier-mediated mechanisms. Regional differences in drug absorption is the main focus on two new PhD projects started at the department in April 2013 within the OrBiTo project.

Members of the group during 2015

Hans Lennernäs, Professor

Bertil Abrahamsson, Professor in industrial biopharmaceutics

Erik Sjögren, Ph.D, Research scientist

Emelie Ahnfelt, PhD Student

David Dahlgren, PhD Student

Ilse Dubbelboer, PhD Student

Elsa Lilienberg, PhD Student

Carl Roos, PhD Student

Johanna Eriksson, PhD Student

Publications, reviews and book chapters 2015

1. Johannsson G, Falorni A, Skrtic S, Lennernäs H, Quinkler M, Monson JP, Stewart PM. Adrenal insufficiency: review of clinical outcomes with current glucocorticoid replacement therapy. *Clin Endocrinol (Oxf)*. 2015, 82 (1): 2-11.
2. Dahlgren D, Roos C, Sjögren E, Lennernäs H. Direct In Vivo Human Intestinal Permeability (Peff) Determined with Different Clinical Perfusion and Intubation Methods. *J Pharm Sci*. 2015 104(9) : 2702-26.
3. Ahnfelt E, Sjögren E, Axén N, Lennernäs H. A miniaturized in vitro release method for investigating drug-release mechanisms. *Int J Pharm*. 2015; 486 (1-2) :339-49
4. Sjögren E, Dahlgren D, Roos C, Lennernäs H. Human in vivo regional intestinal permeability: quantitation using site-specific drug absorption data. *Mol Pharm*. 2015 Jun 1;12(6):2026-39
5. Olivares-Morales A, Lennernäs H, Aarons L, Rostami-Hodjegan A. Translating Human Effective Jejunal Intestinal Permeability to Surface-Dependent Intrinsic Permeability: a Pragmatic Method for a More Mechanistic Prediction of Regional Oral Drug Absorption. *AAPS J*. 2015 17 (5) :1177-92.
6. Malm-Erjefält M, Ekblom M, Vouis J, Zdravkovic M, Lennernäs H. Effect on the Gastrointestinal Absorption of Drugs from Different Classes in the Biopharmaceutics Classification System, When Treating with Liraglutide. *Mol Pharm*. 2015 2; 12(11):4166-73
7. Söderlind E, Abrahamsson B, Erlandsson F, Wanke C, Iordanov V, von Corswant C. Validation of the IntelliCap® system as a tool to evaluate extended release profiles in human GI tract using metoprolol as model drug. *J Control Release*. 2015 Nov 10;217:300-7,
8. Gajendran J, Krämer J, Shah VP, Langguth P, Polli J, Mehta M, Groot DW, Cristofolletti R, Abrahamsson B, Dressman JB. Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Nifedipine. *J Pharm Sci*. 2015 Oct;104(10):3289-98.
9. Kindgen S, Wachtel H, Abrahamsson B, Langguth P. Computational Fluid Dynamics Simulation of Hydrodynamics and Stresses in the PhEur/USP Disintegration Tester Under Fed and Fasted Fluid Characteristics. *J Pharm Sci*. 2015 Sep;104(9):2956-68
10. Vong LB, Mo J, Abrahamsson B, Nagasaki Y. Specific accumulation of orally administered redox nanotherapeutics in the inflamed colon reducing inflammation with dose-response efficacy. *J Control Release*. 2015 Jul 28;210:19-25.
11. Wang Y, Abrahamsson B, Lindfors L, Brasseur JG. Analysis of Diffusion-Controlled Dissolution from Polydisperse Collections of Drug Particles with an Assessed Mathematical Model. *J Pharm Sci*. 2015 Sep;104(9):2998-3017.
12. Lindfors L, Jonsson M, Weibull E, Brasseur JG, Abrahamsson B. Hydrodynamic Effects on Drug Dissolution and Deaggregation in the Small Intestine-A Study with Felodipine as a Model Drug. *J Pharm Sci*. 2015 Sep;104(9):2969-76.
13. Berthelsen R, Holm R, Jacobsen J, Kristensen J, Abrahamsson B, Müllertz A. Kolliphor surfactants affect solubilization and bioavailability of fenofibrate. Studies of in vitro digestion and absorption in rats. *Mol Pharm*. 2015 Apr 6;12(4):1062-71.

14. Petruševska M, Berglez S, Krisch I, Legen I, Megušar K, Peternel L, Abrahamsson B, Cristofolletti R, Groot DW, Kopp S, Langguth P, Mehta M, Polli JE, Shah VP, Dressman J. Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms: Levetiracetam. *J Pharm Sci.* 2015 Sep;104(9):2676-87.
15. Christiansen ML, Müllertz A, Garmer M, Kristensen J, Jacobsen J, Abrahamsson B, Holm R. Evaluation of the use of Göttingen minipigs to predict food effects on the oral absorption of drugs in humans. *J Pharm Sci.* 2015 Jan;104(1):135-43.
16. Fagerberg JH, Sjögren E, Bergström CA. Concomitant intake of alcohol may increase the absorption of poorly soluble drugs. *Eur J Pharm Sci.* 2015 Jan 25;67:12-20
17. Lilienberg, E. Biopharmaceutical Evaluation of Intra-arterial Drug-Delivery Systems for Liver Cancer - Investigations in healthy pigs and liver cancer patients, Thesis, Uppsala: Acta Universitatis Upsaliensis, 2015.

Publications, reviews and book chapters 2014

18. Barker, R, Abrahamsson, B and Kruusmägi, M. Application and validation of an advanced gastrointestinal in vitro model for the evaluation of drug product performance in pharmaceutical development. *Journal of Pharmaceutical Sciences*, 2014, 103, 3704.
19. Berthelsen, R, Sjögren, E, Jacobsen, J, Kristensen, J, Holm, R, Abrahamsson, B and Müllertz, A. Combining in vitro and in silico methods for better prediction of surfactant effects on the absorption of poorly water soluble drugs-a fenofibrate case example. *International Journal of Pharmaceutics*, 2014, 473 (1-2), 356.
20. Carlert, S, Lennernäs, H and Abrahamsson, B. Evaluation of the use of Classical Nucleation Theory for predicting intestinal crystalline precipitation of two weakly basic BSC class II drugs. *European Journal of Pharmaceutical Sciences*, 2014, 53, 17.
21. Charoo, NA, Shamsheer, AA, Lian, LY, Abrahamsson, B, Cristofolletti, R, Groot, DW, Kopp, S, Langguth, P, Polli, J, Shah, VP and Dressman, J. Biowaiver monograph for immediate-release solid oral dosage forms: bisoprolol fumarate. *Journal of Pharmaceutical Sciences*, 2014, 103, 378.
22. Charoo, N, Cristofolletti, R, Graham, A, Lartey, P, Abrahamsson, B, Groot, DW, Kopp, S, Langguth, P, Polli, J, Shah, VP and Dressman, J. Biowaiver Monograph for Immediate-Release Solid Oral Dosage Forms: Fluconazole. *Journal of Pharmaceutical Sciences*, 2014. doi: 10.1002/jps.24181.
23. Christiansen, ML, Holm, R, Kristensen, J, Kreilgaard, M, Jacobsen, J, Abrahamsson, B and Müllertz, A. Cinnarizine food-effects in beagle dogs can be avoided by administration in a Self Nano Emulsifying Drug Delivery System (SNEDDS). *European Journal of Pharmaceutical Sciences*, 2014, 57, 164.
24. Christophersen, PC, Christiansen, ML, Holm, R, Kristensen, J, Jacobsen, J, Abrahamsson, B and Müllertz, A. Fed and fasted state gastro-intestinal in vitro lipolysis: In vitro in vivo relations of a conventional tablet, a SNEDDS and a solidified SNEDDS. *European Journal of Pharmaceutical Sciences*, 2014, 57, 232.

25. Dahan, A, Wolk, O, Zur, M, Amidon, GL, Abrahamsson, B, Cristofolletti, R, Groot, DW, Kopp, S, Langguth, P, Polli, JE, Shah, VP and Dressman, JB. Biowaiver Monographs for Immediate-Release Solid Oral Dosage Forms: Codeine Phosphate. *Journal of Pharmaceutical Sciences*, 2014, 103, 1592.
26. Dubbelboer, IR, Lilienberg, E, Hedeland, M, Bondesson, U, Piquette-Miller, M, Sjögren, E and Lennernäs, H. The Effects of Lipiodol and Cyclosporin A on the Hepatobiliary Disposition of Doxorubicin in Pigs. *Molecular Pharmaceutics*, 2014, 11 (4), 1301.
27. Dubbelboer, IR, Lilienberg, E, Ahnfelt, E, Sjögren, E, Axén, N, Lennernäs H. Treatment of intermediate stage hepatocellular carcinoma: a review of intrahepatic doxorubicin drug-delivery systems. *Therapeutic Delivery*. 2014, 5 (4), 447.
28. Jain, AK, Söderlind, E, Viridén, A, Schug, B, Abrahamsson, B, Knopke, C, Tajarobi, F, Blume, H, Anschütz, M, Welinder, A, Richardson, S, Nagel, S, Abrahamsén-Alami, S and Weitschies, W. The influence of hydroxypropyl methylcellulose (HPMC) molecular weight, concentration and effect of food on in vivo erosion behavior of HPMC matrix tablets. *Journal of Controlled Release*, 2014, 187, 50.
29. Jesson, G, Brisander, M, Andersson, P, Demirbaker, M, Derand, H, Lennernäs, H and Malmsten, M. Carbon Dioxide-Mediated Generation of Hybrid Nanoparticles for Improved Bioavailability of Protein Kinase Inhibitors. *Pharmaceutical research*, 2014, 31 (3), 694.
30. Johannsson G, Skrtic S, Lennernäs H, Quinkler M, Stewart PM. Improving outcomes in patients with adrenal insufficiency: a review of current and future treatments. *Current Medical Research & Opinion*, 2014, 30 (9), 1833.
31. Kostewicz, ES, Abrahamsson, B, Brewster, M, Brouwers, J, Butler, J, Carlert, S, Dickinson, PA, Dressman, J, Holm, R, Klein, S, Mann, J, McAllister, M, Minekus, M, Muenster, U, Müllertz, A, Verwei, M, Vertzoni, M, Weitschies, W, and Augustijns, P. *In vitro* models for the prediction of *in vivo* performance of oral dosage forms. *European Journal of Pharmaceutical Sciences*, 2014, 57C, 342.
32. Lennernäs, H. Regional intestinal drug permeation : Biopharmaceutics and drug development. *European Journal of Pharmaceutical Sciences*, 2014, 57 (SI), 333.
33. Lennernäs, H. Human in Vivo Regional Intestinal Permeability : Importance for Pharmaceutical Drug Development. *Molecular Pharmaceutics*, 2014, 11 (1), 12.
34. Lennernäs, H, Aarons, L, Augustijns, P, Beato, S, Bolger, M, Box, K, Brewster, M, Butler, J, Dressman, J, Holm, R, Frank, KJ, Kendall, R, Langguth, P, Sydor, J, Lindahl, A, McAllister, M, Muenster, U, Mullertz, A, Ojala, K, Pepin, X, Reppas, C, Rostami-Hodjegan, A, Verwei, M, Weitschies, W, Wilson, C, Karlsson, C and Abrahamsson, B. Oral biopharmaceutics tools - Time for a new initiative - An introduction to the IMI project OrBiTo. *European Journal of Pharmaceutical Sciences*, 2014, 57 (SI), 292.
35. Lennernäs H, Abrahamsson P, Langguth B. Oral biopharmaceutics-current status and identified gaps of understanding. *European Journal of Pharmaceutical Sciences*, 2014, 57, 98.

36. Lennernäs, H, Langguth, P, Yamashita, S and Crommelin, DJA. Theme Issue 5th World Conference on Drug Absorption, Transport and Delivery. *European Journal of Pharmaceutical Sciences*, 2014, 61, 1.
37. Lilienberg, E, Ebeling-Barbier, C, Nyman, R, Hedeland, M, Bondesson, U, Axén, N and Lennernäs, H. Investigation of Hepatobiliary Disposition of Doxorubicin Following Intrahepatic Delivery of Different Dosage Forms. *Molecular Pharmaceutics*, 2014, 11 (1), 131.
38. Lundahl, A, Åberg, AT, Bondesson, U, Lennernäs, H and Hedeland, M. High-resolution mass spectrometric investigation of the phase I and II metabolites of finasteride in pig plasma, urine and bile. *Xenobiotica*, 2014, 44 (6), 798.
39. Nilsson, AG, Marelli, C, Fitts, D, Bergthorsdottir, R, Burman, P, Dahlqvist, P, Ekman, B, Engstrom, BE, Olsson, T, Ragnarsson, O, Ryberg, M, Wahlberg, J, Lennernäs, H, Skrtic, S and Johannsson, G. Prospective evaluation of long-term safety of dual-release hydrocortisone replacement administered once daily in patients with adrenal insufficiency. *European Journal of Endocrinology*, 2014, 171 (3), 369.
40. Selen, A, Dickinson, PA, Mullertz, A, Crison, JR, Mistry, HB, Cruanes, M, Martinez, MN, Lennernäs, H, Wigal, TL, Swinney, DC, Polli, JE, Serajuddin, ATM, Cook, JA and Dressman, JB. The Biopharmaceutics Risk Assessment Roadmap for Optimizing Clinical Drug Product Performance. *Journal of Pharmaceutical Sciences*, 2014, 103 (11), 3377.
41. Shohin, IE, Kulinich, JI, Ramenskaya, GV, Abrahamsson, B, Kopp, S, Langguth, P, Polli, JE, Shah, VP, Groot, DW, Barends, DM and Dressman, JB. Biowaiver monographs for immediate release solid oral dosage forms: piroxicam. *Journal of Pharmaceutical Sciences*, 2014, 103, 367.
42. Sjögren, E, Abrahamsson, B, Augustijns, P, Becker, D, Bolger, MB, Brewster, M, Brouwers, J, Flanagan, T, Harwood, M, Heinen, C, Holm, R, Juretschke, H-P, Kubbinga, M, Lindahl, A, Lukacova, V, Munster, U, Neuhoff, S, Nguyen, MA, van Peer, A, Reppas, C, Hodjegan, AR, Tannergren, C, Weitschies, W, Wilson, C, Zane, P, Lennernäs, H and Langguth, P. In vivo methods for drug absorption - Comparative physiologies, model selection, correlations with in vitro methods (IVIVC), and applications for formulation/API/excipient characterization including food effects. *European Journal of Pharmaceutical Sciences*, 2014, 57, 99.
43. Sjögren, E, Hedeland, M, Bondesson, U and Lennernäs, H. Effects of verapamil on the pharmacokinetics and hepatobiliary disposition of fexofenadine in pigs. *European Journal of Pharmaceutical Sciences*, 2014, 57, 214.
44. Sjögren, E, Tammela, TL, Lennernäs, B, Taari, K, Isotalo, T, Malmsten, L-Å, Axén, N and Lennernäs, H. Pharmacokinetics of an Injectable Modified-Release 2-Hydroxyflutamide Formulation in the Human Prostate Gland Using a Semiphysiologically Based Biopharmaceutical Model. *Molecular Pharmaceutics*, 2014, 11 (9), 3097.
45. Smith, D, Artursson, P, Avdeef, A, Di, L, Ecker, GF, Faller, B, Houston, JB, Kansy, M, Kerns, EH, Kramer, SD, Lennernäs, H, van de Waterbeemd, H, Sugano, K and Testa, B. Passive Lipoidal Diffusion and Carrier-Mediated Cell Uptake Are Both Important Mechanisms of Membrane Permeation in Drug Disposition. *Molecular Pharmaceutics*, 2014, 11 (6), 1727.

46. Sousa, T, Yadav, V, Zann, V, Borde, A, Abrahamsson, B and Basit, AW. On the Colonic Bacterial Metabolism of Azo-Bonded Prodrugsof 5-Aminosalicylic Acid. *Journal of Pharmaceutical Sciences*, 2014, 103, 3171.
47. Tannergren, C, Borde, A, Boreström, C, Abrahamsson, B and Lindahl, A. Evaluation of an in vitro faecal degradation method for early assessment of the impact of colonic degradation on colonic absorption in humans. *European Journal of Pharmaceutical Sciences*, 2014, 57, 200.

Publications, reviews and book chapters 2013

1. Matsson, EM, Eriksson, UG, Palm, JE, Artursson, P, Karlgren, M, Lazorova, L, Brannstrom, M, Ekdahl, A, Duner, K, Knutson, L, Johansson, S, Schutzer, K-M and Lennernäs, H. Combined in Vitro-in Vivo Approach To Assess the Hepatobiliary Disposition of a Novel Oral Thrombin Inhibitor. *Molecular Pharmaceutics*, 2013, 10 (11), 4252.
2. Sjögren, E, Westergren, J, Grant, I, Hanisch, G, Lindfors, L, Lennernäs, H, Abrahamsson, B and Tannergren, C. In silico predictions of gastrointestinal drug absorption in pharmaceutical product development: Application of the mechanistic absorption model GI-Sim. *European Journal of Pharmaceutical Sciences*, 2013, 49 (4), 679.
3. Larsen, AT, Åkesson, P, Juréus, A, Saaby, L, Abu-Rmaileh, R, Abrahamsson, B, Østergaard, J and Müllertz, A. Bioavailability of cinnarizine in dogs: effect of SNEDDS loading level and correlation with cinnarizine solubilization during in vitro lipolysis. *Pharmaceutical Research*, 2013, 30 (12), 3101.
4. Soares, KC, Rediguieri, CF, Souza, J, Serra, CH, Abrahamsson, B, Groot, DW, Kopp, S, Langguth, P, Polli, JE, Shah, VP and Dressman, J. Biowaiver monographs for immediate-release solid oral dosage forms: Zidovudine (azidothymidine). *Journal of Pharmaceutical Sciences*, 2013, 102 (8), 2409.
5. Larsen, AT, Ohlsson, AG, Polentarutti, B, Barker, RA, Phillips, AR, Abu-Rmaileh, R, Dickinson, PA, Abrahamsson, B, Ostergaard, J and Müllertz, A. Oral bioavailability of cinnarizine in dogs: relation to SNEDDS droplet size, drug solubility and in vitro precipitation. *European Journal of Pharmaceutical Sciences*, 2013, 23, 48 (1-2), 339.
6. Cristofolletti, R, Nair, A, Abrahamsson, B, Groot, DW, Kopp, S, Langguth, P, Polli, JE, Shah, VP and Dressman, JB. Biowaiver monographs for immediate release solid oral dosage forms: efavirenz. *Journal of Pharmaceutical Sciences*, 2013, 102 (2), 318.

Funding

The group receives funding from the Swedish Research Council, Innovative Medicine Initiative and Pharmaceutical Industry.

Presentations at symposia and congresses 2015

1. Lilienberg, E., Dubbelboer, I.R. Bondesson, U., Hedeleand, M., Karalli, A., Stål, P., Ebeling Barbier, C., Norén, A., Duraj, F., Nyman, R., Sjögren, E., Lennernäs, H. Interim analysis – drug eluting beads vs. lipiodol-based emulsion in patients with hepatocellular carcinoma. CRS Annual Meeting and Exposition, June 26-29, 2015, Edinburgh, Scotland.
2. Lilienberg, E. The role of the formulation on the hepatobiliary disposition of doxorubicin and doxorubicinol in vivo. Drug Processing and Delivery meeting, May 6, 2015, Uppsala, Sweden
3. Dubbelboer, I.R. Oral presentation: Liver targeted drug delivery systems: Improved understanding by use of PBBP modeling. 4th annual Nordforsk FFTP network meeting. January 22 2015, Copenhagen, Denmark.
4. Dubbelboer, I.R, Lilienberg, E, Sjögren, E, and Lennernäs H. Poster: Application of a PBBP model to liver targeted drug delivery systems. 42nd CRS Annual meeting. July 26-29 2015, Edinburgh, Scotland.
5. Lennernäs H. Local and focal drug delivery systems: future treatment options to improve benefit:safety ratio. Swedish Pharmaceutical Association, Scheele Award Symposium, November 2015
6. Ahnfelt, E., Sjögren, E., Axén, N., Lennernäs, H. In vivo predictive ability of two selected in vitro methods applied on DC Bead. CRS Annual Meeting and Exposition, June 26-29, 2015, Edinburgh, Scotland.
7. Dahlgren, David; Roos, Carl; Lundqvist, Anders; Abrahamsson, Bertil; Hellström, Per; Sjögren, Erik; Lennernäs, Hans. Human in vivo regional intestinal permeability: Quantitation using site-specific drug absorption data. CRS Annual Meeting and Exposition, June 26-29, 2015, Edinburgh, Scotland.
8. Dahlgren, David; Roos, Carl; Sjögren, Erik; Lennernäs, Hans. Direct In Vivo Human Intestinal Permeability (Peff) Determined with Different Clinical Perfusion and Intubation Methods. PhysChem Forum, UK
9. Dahlgren, David; Roos, Carl; Sjögren, Erik; Lennernäs, Hans. The Serosal Layer's Potential Impact On Rat Intestinal Tissue Viability And Permeability. CRS Annual Meeting and Exposition, June 26-29, 2015, Edinburgh, Scotland.

Patents and patents applications

More than 15 patents and patents applications..

Drug Delivery

Professor Per Artursson

Drug Delivery Group

In 2015, the drug delivery group developed in several positive ways. These included new recruitments, continued contributions in top ranked journals, a healthy flow of publications in our own fields and new grants to our younger scientists.

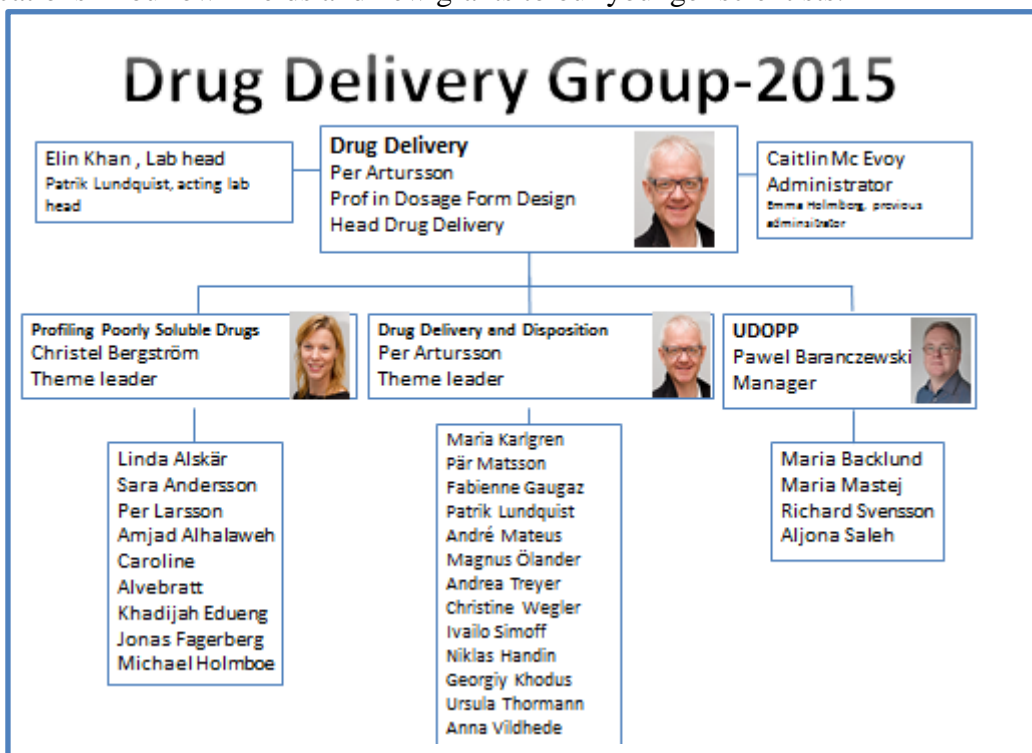


Fig 1. The drug delivery group in 2015

The research in the drug delivery group is divided into three collaborating domains, fig 1. In the first domain (Drug Transport and Disposition), headed by Dr Artursson, the focus is on predictive pharmacokinetics, where special attention is given to the effects of transport proteins on drug disposition. In the second domain (Profiling Poorly Soluble Drugs), headed by Dr Bergström, the focus is on predictive biopharmaceutics, with a focus on drug formulation, solubility and dissolution. In the third domain (UDOPP), headed by Dr Baranczewski, the knowledge of the research groups is combined with complementary expertise from the pharmaceutical industry in e.g. drug metabolism, medicinal chemistry, PBPK modelling and bioanalysis. Together, the three domains provide all expertise required for a state-of-the-art collaborative platform for compound profiling. To summarize, the drug delivery research group takes a multidisciplinary approach that combines computational chemistry and bioinformatics with cell- and molecular biology, biopharmaceutics, pharmaceuticals and physical chemistry. The research delivers computational and experimental models for studies of important mechanisms of drug delivery in the human body.

Drug Delivery and Disposition

The drug transport and disposition group continued to investigate transport mechanisms in human intestine and liver, two of the most important organs determining drug absorption and distribution in man. New more sensitive equipment and methodologies, partly co-developed with our collaborators at the Max-Planck Institute of Biochemistry, Martinsried, Germany, allowed quantification of the global proteome without tissue or cell fractionation at an unsurpassed level. Importantly, this eliminated the large errors introduced by subcellular fractionation (since there are no “pure” subcellular fractions). In our own laboratory, multiplexed targeted proteomics were set up, allowing simultaneous determination of about 15 drug transporting proteins and 15 drug metabolizing enzymes. Both global and targeted proteomics are now used in our “bottom-up” efforts to model of drug fate.

During the last year, a shift in our modelling efforts from more static models providing snapshots of drug distribution, to mechanistic models that integrate drug and metabolite fate over time. In one of the (system) models, we quantified the global (transporter) proteome of the intestinal epithelium. When combined with our large database of kinetic drug transport parameters, the total transport protein activity could be modelled and compared with the transport characteristics observed in man. The goal was to investigate if the transport protein activity would be sufficient to explain all transport across cellular barriers as has been recently speculated, but not proven. Our data showed that the intestinal transport protein activity is not always sufficient to explain the rapid absorption of many drugs and those other mechanisms such as passive permeability dominates in these cases, fig 2. In another study we collaborated with the department of pharmaceutical biosciences to develop a bottom up model for drug transport across the human hepatocyte. This allowed us quantify the contribution eight uptake and efflux transporters to the blood-to-bile flux of statins for the first time.

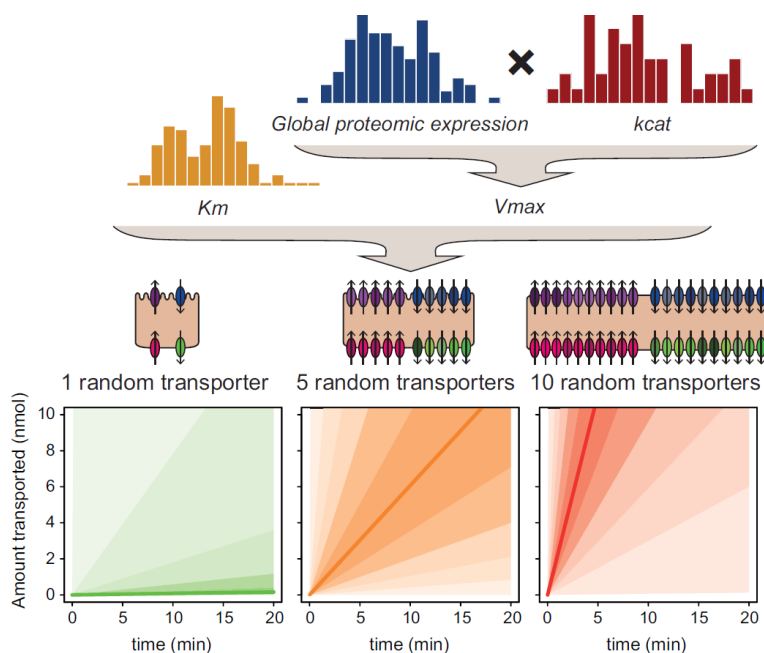


Fig 2. Principle for modelling the total transport activity across the human intestinal epithelium. The three graphs at the bottom show the transport protein-mediated rates that would result from one (green),

five (orange), or ten (red) transporters, each with expression levels and kinetic values randomly selected from the frequency distributions graphs at the top.

Further, our recently introduced small-scale model for determination of free intracellular concentrations of drugs and metabolites was applied in the pharmacology field. We could show that the intracellular free concentration of a drug or its active metabolite correlates both with engagement of the target itself (*Nat. Commun*, accepted) and with far from target endpoints, such as cell growth arrest. Our findings suggest that our method can be used to predict the often unexpected and unexplained drop off in effect observed in drug discovery for drugs acting on intracellular targets. Our assay is already set up by big pharma companies and is also available at our profiling platform.

Profiling Poorly Soluble Drugs

The research performed within Dr Bergström's group is focused on poorly soluble compounds, and in particular on the delivery of these in orally administered dosage forms. Formulation strategies currently being explored are amorphization, lipid-based drug delivery systems and mesoporous drug carriers. During 2015 we embarked on two new EU/ERC projects. In the ERC project INTESTINANOS we target the development of a virtual intestine for simulation of drug solubilization, supersaturation and precipitation. The project characterizes aspirated intestinal fluid in the fasted and fed state through the use of sensitive analytical equipment. The obtained data are used as the comparator for in silico developed intestinal fluids, obtained from Molecular Dynamics (MD) simulations. In the EU-JPIAMR project Senbiotar we collaborate with University of Nottingham, University of Copenhagen and Laval University to develop new antibiotics efficient in the treatment of respiratory infections of patients with cystic fibrosis. These new projects have resulted in a significant growth of the group, which by the end of 2015 consisted of four PhD students and two post docs, with the recruitment of two additional post docs and one PhD student being finalized (start in January 2016).

While these two projects are in the early days with results expected to emerge during 2016, we have also continued our efforts to better predict formulate-ability. Papers were published addressing all three strategies being explored (amorphization, mesoporous material and lipid-based formulation (LBF)); here some recent data from the LBF project are described in detail. Identification of the usefulness of LBFs for delivery of poorly water-soluble drugs is at date mainly experimentally based. In a recent paper, we used a diverse drug dataset, and more than 2,000 equilibrium solubility measurements to develop experimental and computational tools to predict the loading capacity of LBFs, i.e. the maximum amount of drug that can be dissolved in LBFs. Computational models were developed to enable in silico prediction of this property. For the first time, loading capacity in complex formulations was accurately predicted using multivariate data analysis of molecular information extracted from calculated descriptors and thermal properties of the crystalline drug. The analysis also revealed three optimal physicochemical properties for drug solubility in lipids: the drugs should be neutral or basic, have a T_m below 150°C, and few polar groups.

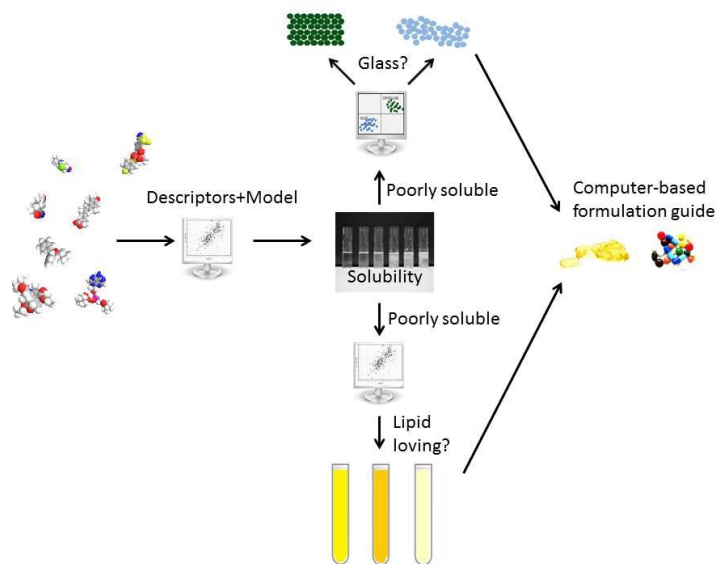


Figure 3. Computer-based tools are used to extract molecular information that can be used to predict solubility in water-based systems including intestinal fluid. For poorly soluble compounds different *in silico* models have been developed by the group; these can be used to predict whether amorphization or lipid-based formulations are likely to be successful formulation strategies to support intestinal absorption and enable oral delivery of such compounds.

Uppsala Drug Optimization and Pharmaceutical Profiling Platform (UDOPP)

Uppsala Drug Optimization and Pharmaceutical Profiling Platform (UDOPP) has three main branches consisting of facilities that are founded as collaborations within other platforms. The oldest branch is the UDOPP-CBCS facility within the Chemical Biology Consortium Sweden (CBCS), which started in 2010. The other two branches of UDOPP are ADMEoT, a facility within SciLifeLab's Drug Discovery and Development Platform (DDD-P), and In Vitro ADME facility within the European Gram-Negative Antibacterial Engine Consortium (ENABLE) at the Innovative Medicine Initiative (IMI), both established in 2014. The three facilities combine efforts to provide physicochemical profiling, *in vitro* ADME (absorption, distribution, metabolism, excretion) and pharmacokinetics expertise more effectively in order to deliver compound profiling and pharmacokinetics services which enables the selection of high quality compounds for chemical biology and drug discovery. During 2015, the UDOPP team consisted of five persons with broad scientific background and more the 50 years of academic and industrial experience. UDOPP has contributed to a substantial number of ADME investigations and pharmaceutical profiling projects during 2015. Within CBCS about 20 projects in total have received contribution of UDOPP expertise. For the DDD-P, the ADMEoT facility contributed to 7 full and 8 service drug discovery projects and for the IMI/ENABLE initiative 9 projects was supported by UDOPP during the year.

During 2015 UDOPP have contributed significantly to the development of new lipoprotein lipase agonists together with researchers at Umeå University. Poor pharmacokinetics was overcome by a successful lead optimization strategy. Another project was published together with scientists at Uppsala University and Karolinska Institutet which aimed at describing the ADME properties of substituted Sulfonimidamides as acid bioisosteres. This functional group was found to have promising characteristics and give researchers new opportunities for drug design. To increase capacity and quality within UDOPP, automation and work flow of basic ADME assays (solubility, protein binding and metabolic stability) was fully implemented in 2015. Additionally, in collaboration with the drug delivery group,

new CRISPR-Cas9 optimized cell lines for routine use in drug permeability and drug efflux studies was evaluated at the platform.

Drug Delivery Group Members 2015

Per Artursson, Professor

Pawel Baranczewski, Research Scientist

Christel Bergström, Associate Professor

Amjad Alhalaweh, Research Scientist

Linda Alskär, PhD Student

Caroline Alvebratt, PhD Student

Sara Andersson, PhD Student

Maria Backlund, Research Scientist

Khadijah Edueng, PhD Student

Fabienne Gagauz, Post doc

Niklas Handin, PhD Student

Michael Holmboe, Post doc

Jonas Fagerberg, PhD

Elin Khan, M Pharm

Georgiy Khodus, Research Scientist

Per Larsson, Research Scientist

Patrik Lundquist, Research Scientist

Maria Mastej, BSc

Pär Matsson, Assistant Professor

André Mateus, PhD Student

Aljona Saleh, Research Scientist

Ivailo Simoff, Research Scientist

Richard Svensson, Research Scientist

Ursula Thormann, Post Doc

Andrea Treyer, PhD Student

Anna Vildhede, PhD

Christine Wegler, PhD Student

Magnus Ölander, PhD Student

Caitlin McEvoy, Administrator

Emma Holmberg, Administrator

Publications, reviews and book chapters 2015

1. Alhalaweh, A., Alzghoul, A., Mahlin, D., Bergström, C.A.S. Physical stability of drugs after storage above and below the glass transition temperature: Relationship to glass-forming ability. *International journal of pharmaceutics*. 2015, 95 (1), 312-317.
2. Alskär, LC., Bergström CAS. Models for Predicting Drug Absorption From Oral Lipid-Based Formulations. *Current Molecular Biology Reports*. 2015, 1 (4), pp 141-147.
3. Alskär, LC., Porter, JH., Bergström CAS. Tools for Early Prediction of Drug Loading in Lipid-Based Formulations. *Mol. Pharm.* Publication Date (Web): November 15, 2015. DOI:10.1021/acs.molpharmaceut.5b00704
4. Artursson, P., Knight, S.D. Breaking the intestinal barrier to deliver drugs. 2015. *Science*, 347, 716-717.
5. Borhade, S.R., Svensson, R., Brandt, P., Artursson, P., Arvidsson, P.I., Sandström, A. Preclinical Characterization of Acyl Sulfonimidamides: Potential Carboxylic Acid Bioisosteres with Tunable Properties. *ChemMedChem*. 2015, 10 (3), 455-60.
6. Caraballo, R. , Larsson, M., Nilsson, S.K., Ericsson, M., Qian, W., Tran, N.P., Kindahl, T. , Svensson, R., Artursson, P., Olivecrona, G., Enquist, P-A. and Elofsson, M. Structure-activity relationships for lipoprotein lipase agoists that lower plasma triglycerides *in vivo*. *Eur J Med Chem*. 2015, (103). 191-209.
7. Cho, W., Kim, M.K., Jung, M. K., Park, J., Cha, K.H., Kim, J.S., Park, H. J., Alhalaweh, A., Velaga P. S., Hwang S.J.. Design of salmon calcitonin particles for nasal delivery using spray-drying and novel supercritical fluid-assisted spray-drying processes. *International journal of pharmaceutics*. 2015, 478 (1), 288–296.
8. Fagerberg E, Sjögren E., Bergström C.A.S. Concomitant Intake of Alcohol May Increase the Absorption of Poorly Soluble Drugs. *European Journal of Pharmaceutical Sciences*, 2015, 67, 12-20.
9. Fagerberg J.H. and Bergström C.A.S. Intestinal solubility and absorption of poorly water-soluble drugs: predictions, challenges and solutions. *Therapeutic Delivery*, 2015, 6(8), 935-959.
10. Fagerberg JH, Karlsson E, Ulander J, Hanisch G, Bergström CAS. Computational Prediction of Drug Solubility in Fasted Simulated and Aspirated Human Intestinal Fluid. *Pharmaceutical Research* 2015, 32(2), 578-589.
11. Gordon L.J., Allen M., Artursson P., Hann M.M., Leavens B.J., Mateus A., Readshaw S., Valko K., Wayne G.J., West A. Direct Measurement of Intracellular Compound Concentration by Rapid Fire Mass Spectrometry Offers Insights into Cell Permeability. *J Biomol Screen*, 2015 1-9.
12. Karlgren M. and Bergström C.A.S. How physicochemical properties of drugs affect their metabolism and clearance. In *New Horizons in Metabolism*, Ed Alan Wilson, The Royal Society of Chemistry, UK, 2015.

13. Matsson P, Bergström CA. Computational modeling to predict the function and impact of drug transporters. *In Silico Pharmacol.* 2015 (3)8. doi:10.1186/s40203-015-0012-3
14. Matsson, P, Fenu, LA, Lundquist, P, Kansy, M and Artursson, P. Quantifying the impact of transporters on cellular drug permeability, *Trends Pharmacol Sci.* 2015, 36 (5), 255-62.
15. Matsson P, Fenu LA, Lundquist P, Wiśniewski JR, Kansy M, Artursson P. Addendum to 'Quantifying the impact of transporters on cellular drug permeability'. *Trends Pharmacol Sci.* 2015, 36(9):559.
16. Simoff, I, Karlren, M, Backlund, M, Lindström, A-C, Gaugaz, FZ, Matsson, P, Artursson, A. Complete Knockout of Endogenous Mdl1 (*Abcb1*) in MDCK Cells by CRISPR-Cas9. *J of Pharm Sci.* Epub ahead of print. 2015.
17. Schwoen, K.B., Schowen, R.L., Borchardt, S.E., Borchardt, P.M., Artursson, P., Audus, K.L., Augustijns, P., Nicolazzo, J.A., Raub, T.J., Takakura, Y., Thakker, D.R., Schöneich, C., Siahaan, T.J. and Wolfe, M.S. A Tribute to Ronald T. Borchardt - Teacher, Mentor, Scientist, Colleague, Leader, Friend and Family Man *J of Pharm Sci.* Epub ahead of print. 2015.
18. Shojaee, S., Nokhodchi, A., Cumming, I., Alhalaweh, A., Kaialy, W. Investigation of drug release from PEO tablet matrices in the presence of vitamin E as antioxidant. *Current drug delivery.* 2015, 12(5):591-599.
19. Vildhede A., Wisniewski J.R., Norén A., Karlgren M., Artursson P. Comparative proteomic analysis of human liver tissue and isolated hepatocytes with a focus on proteins determining drug exposure. *J Proteome Res.* 2015, 14 (8), 305-14.
20. Wiśniewski, J. R., Gaugaz, F. Z., Fast and Sensitive Total Protein and Peptide Assays for Proteomic Analysis. *Anal. Chem.* 2015, 87 (8), 4110-4116.
21. Zhang P., Zardán Gómez de la Torre T., Forsgren J. Bergström C.A.S., Strømme M. Diffusion-controlled drug release from the mesoporous magnesium carbonate Upsalite®. *Journal of Pharmaceutical Sciences*, e-pub June 18, 2015.
22. Ölander, M, Wisniwski, JR, Matsson, P, Lundquist, P, Artursson, P. The Proteome of Filter-Grown Caco-2 Cells With a Focus on Proteins Involved in Drug Disposition. *J of Pharm Sci.* Epub ahead of print. 2015.

Publications, reviews and book chapters 2014

1. Alhalaweh, A, Alzghoul, A, Kaialy, W, Mahlin, D and Bergström, CAS. Computational predictions of glass-forming ability and crystallization tendency of drug molecules. *Molecular Pharmaceutics*, 2014, 11 (9), 3123.
2. Alzghoul A, Alhalaweh A, Mahlin D, Bergström CA. Experimental and computational prediction of glass transition temperature of drugs. *J Chem Inf Model.* 2014, 22;54(12), 3396-403
3. Bergström, CAS, Andersson, SBE, Fagerberg, JH, Ragnarsson, G and Lindahl, A. Is the full potential of the biopharmaceutics classification system reached? *European Journal of Pharmaceutical Sciences*, 2014, 57, 224.
4. Bergström, CAS, Holm, R, Jorgensen, SA, Andersson, SBE, Artursson, P, Beato, S, Borde, A, Box, K, Brewster, M, Dressman, J, Feng, K-I, Halbert, G,

- Kostewicz, E, McAllister, M, Muenster, U, Thinnes, J, Taylor, R and Mullertz, A. Early pharmaceutical profiling to predict oral drug absorption : Current status and unmet needs. *European Journal of Pharmaceutical Sciences*, 2014, 57, 173.
5. Englund, G, Lundquist, P, Skogastierna, C, Johansson, J, Hoogstraate, J, Afzelius, L, Andersson, TB and Projean, D. Cytochrome P450 Inhibitory Properties of Common Efflux Transporter Inhibitors. *Drug Metabolism And Disposition*, 2014, 42 (3), 441.
 6. Ferrins, L, Gazdik, M, Rahmani, R, Rahmani, R, Sykes, ML, Jones, AJ, Avery, VM, White, KL, Ryan, E, Charman, SA, Kaiser, M, Bergström, CAS and Baell, JB. Pyridyl Benzamides as a Novel Class of Potent Inhibitors for the Kinetoplastid *Trypanosoma brucei*. *Journal of Medicinal Chemistry*, 2014, 57 (15), 6393.
 7. Fransson, R, Nordvall, G, Bylund, J, Carlsson-Jonsson, A, Kratz, JM, Svensson, R, Artursson, P, Hallberg, M and Sandström, A. Exploration and pharmacokinetic profiling of phenylalanine based carbamates as novel substance p 1-7 analogues. *ACS Medicinal Chemistry Letters*, 2014, 5 (12), 1272.
 8. Gad, H, Koolmeister, T, Jemth, A-S, Eshtad, S, Jacques, SA, Strom, CE, Svensson, LM, Schultz, N, Lundback, T, Einarsdottir, BO, Saleh, A, Gokturk, C, Baranczewski, P, Svensson, R, Berntsson, RP-A, Gustafsson, R, Stromberg, K, Sanjiv, K, Jacques-Cordonnier, M-C, Desroses, M, Gustavsson, A-L, Olofsson, R, Johansson, F, Homan, EJ, Loseva, O, Brautigam, L, Johansson, L, Hoglund, A, Hagenkort, A, Pham, T, Altun, M, Gaugaz, FZ, Vikingsson, S, Evers, B, Henriksson, M, Vallin, KSA, Wallner, OA, Hammarstrom, LGJ, Wiita, E, Almlof, I, Kalderen, C, Axelsson, H, Djureinovic, T, Puigvert, JC, Haggblad, M, Jeppsson, F, Martens, U, Lundin, C, Lundgren, B, Granelli, I, Jensen, AJ, Artursson, P, Nilsson, JA, Stenmark, P, Scobie, M, Berglund, UW and Helleday, T. MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool. *Nature*, 2014, 508 (7495), 215.
 9. Gaugaz, F. Z., Redondo-Horcajo, M., Barasoain, I., Díaz, J. F., Cobos-Correa, A., Kaufmann, M., Altmann, K.-H. The Impact of Cyclopropane Configuration on the Biological Activity of Cyclopropyl-Epothilones. *ChemMedChem*. 2014, 9, 2227-32.
 10. Gising, J, Belfrage, AK, Alogheli, H, Ehrenberg, A, Åkerblom, E, Svensson, R, Artursson, P, Karlén, A, Danielsson, UH, Larhed, M and Sandström, A. Achiral Pyrazinone-Based Inhibitors of the Hepatitis C Virus NS3 Protease and Drug-Resistant Variants with Elongated Substituents Directed Toward the S2 Pocket. *Journal of Medicinal Chemistry*, 2014, 57 (5), 1790.
 11. Kitambi, SS, Toledo, EM, Usoskin, D, Wee, S, Harisankar, A, Svensson, R, Sigmundsson, K, Kalderen, C, Niklasson, M, Kundu, S, Aranda, S, Westermark, B, Uhrbom, L, Andang, M, Damberg, P, Nelander, S, Arenas, E, Artursson, P, Walfridsson, J, Nilsson, KF, Hammarstrom, LGJ and Ernfors, P. Vulnerability of Glioblastoma Cells to Catastrophic Vacuolization and Death Induced by a Small Molecule. *Cell*, 2014, 157 (2), 313.
 12. Lampa, A, Alogheli, H, Ehrenberg, AE, Åkerblom, E, Svensson, R, Artursson, P, Danielson, H, Karlén, A and Sandström, A. Vinylated linear P2 pyrimidinyloxyphenylglycine based inhibitors of the HCV NS3/4A protease and

- corresponding macrocycles. *Bioorganic & Medicinal Chemistry*, 2014, 22 (23), 6595.
13. Lampa, A, Bergman, S, Svahn Gustafsson, S, Alogheli, H, Åkerblom, E, Lindeberg, G, Svensson, R, Artursson, P, Danielsson, HU, Karlén, A and Sandström, A. Novel Peptidomimetic Hepatitis C Virus NS3/4A Protease Inhibitors Spanning the P2–P1' Region. *ACS Medicinal Chemistry Letters*, 2014, 5 (3), 249.
 14. Lundquist, P, Englund, G, Skogastierna, C, Loof, J, Johansson, J, Hoogstraate, J, Afzelius, L and Andersson, TB. Functional ATP-Binding Cassette Drug Efflux Transporters in Isolated Human and Rat Hepatocytes Significantly Affect Assessment of Drug Disposition. *Drug Metabolism And Disposition*, 2014, 42 (3), 448.
 15. Lundquist, P, Loof, J, Fagerholm, U, Sjogren, I, Johansson, J, Briem, S, Hoogstraate, J, Afzelius, L and Andersson, TB. Prediction of In Vivo Rat Biliary Drug Clearance from an In Vitro Hepatocyte Efflux Model. *Drug Metabolism And Disposition*, 2014, 42 (3), 459.
 16. Lundquist, P, Loof, J, Sohlenius-Sternbeck, A-K, Floby, E, Johansson, J, Bylund, J, Hoogstraate, J, Afzelius, L and Andersson, TB. The Impact of Solute Carrier (SLC) Drug Uptake Transporter Loss in Human and Rat Cryopreserved Hepatocytes on Clearance Predictions. *Drug Metabolism And Disposition*, 2014, 42 (3), 469.
 17. Mateus, A, Matsson, P and Artursson, P. A High-Throughput Cell-Based Method to Predict the Unbound Drug Fraction in the Brain. *Journal of Medicinal Chemistry*, 2014, 57 (7), 3005.
 18. Nordmark A, Andersson A, Baranczewski P, Wanag E, Ståhle L. Assessment of interaction potential of AZD2066 using in vitro metabolism tools, physiologically based pharmacokinetic modelling and in vivo cocktail data. *Eur J Clin Pharmacol*. 2014,70(2), 167-78
 19. Over, B, McCarren, P, Artursson, P, Foley, M, Giordanetto, F, Gronberg, G, Hilgendorf, C, Lee, MD, Matsson, P, Muncipinto, G, Pellisson, M, Perry, MWD, Svensson, R, Duvall, JR and Kihlberg, J. Impact of Stereospecific Intramolecular Hydrogen Bonding on Cell Permeability and Physicochemical Properties. *Journal of Medicinal Chemistry*, 2014, 57 (6), 2746.
 20. Pedersen, C, Slepkin, A, Andersson, SBE, Fagerberg, JH, Bergström, CAS and Peterson, EM. Formulation of the Microbicide INP0341 for In Vivo Protection against a Vaginal Challenge by *Chlamydia trachomatis*. *PLoS ONE*, 2014, 9 (10), e110918.
 21. Smith, D, Artursson, P, Avdeef, A, Di, L, Ecker, GF, Faller, B, Houston, JB, Kansy, M, Kerns, EH, Kramer, SD, Lennernäs, H, van de Waterbeemd, H, Sugano, K and Testa, B. Passive Lipoidal Diffusion and Carrier-Mediated Cell Uptake Are Both Important Mechanisms of Membrane Permeation in Drug Disposition. *Molecular Pharmaceutics*, 2014, 11 (6), 1727.
 22. Vildhede, A, Karlgren, M, Svedberg, EK, Wisniewski, JR, Lai, Y, Norén, A and Artursson, P. Hepatic Uptake of Atorvastatin : Influence of Variability in Transporter Expression on Uptake Clearance and Drug-Drug Interactions. *Drug Metabolism And Disposition*, 2014, 42 (7), 1210

Publications, reviews and book chapters 2013

1. Artursson P, Matsson P and Karlgren M In vitro characterization of interactions with drug transporting proteins Transporters in Drug Discovery, Development and Use. Eds: Sugiyama Y, Steffansen B. Springer, Volume 7, 2013, pp 37-65
2. Chu, X, Korzekwa, K, Elsby, R, Fenner, K, Galetin, A, Lai, Y, Matsson, P, Moss, A, Nagar, S, Rosania, GR, Bai, JPF, Polli, JW, Sugiyama, Y and Brouwer, KLR. Intracellular Drug Concentrations and Transporters: Measurement, Modeling, and Implications for the Liver. *Clinical Pharmacology and Therapeutics*, 2013, 94 (1), 126.
3. Fransson, R, Sköld, C, Kratz, JM, Svensson, R, Artursson, P, Nyberg, F, Hallberg, M and Sandström, A. Constrained H-Phe-Phe-NH₂ Analogues With High Affinity to the Substance P 1-7 Binding Site and With Improved Metabolic Stability and Cell Permeability. *Journal of Medicinal Chemistry*, 2013, 56 (12), 4953.
4. Johansson, C-C, Gennemark, P, Artursson, P, Abelo, A, Ashton, M and Jansson-Lofmark, R. Population pharmacokinetic modeling and deconvolution of enantioselective absorption of eflornithine in the rat. *Journal of Pharmacokinetics and Pharmacodynamics*, 2013, 40 (1), 117.
5. Juric, S, Lundquist, P, Hu, Y, Jureus, A and Sohlenius-Sternbeck, AK. The utility of cold-preserved human hepatocytes in studies on cytochrome P450 induction and hepatic drug transport. *Xenobiotica*. 2013, 43 (9), 785.
6. Karunaratne, T, Boström, H and Norinder, U. Comparative analysis of the use of chemoinformatics-based and substructure-based descriptors for quantitative structure-activity relationship (QSAR) modeling. *Intelligent Data Analysis*, 2013, 17 (2), 327.
7. Mahlin, D and Bergström, CAS. Early drug development predictions of glass-forming ability and physical stability of drugs. *European Journal of Pharmaceutical Sciences*, 2013, 49 (2), 323.
8. Mateus, A, Matsson, P and Artursson, P. Rapid Measurement of Intracellular Unbound Drug Concentrations. *Molecular Pharmaceutics*, 2013, 10 (6), 2467.
9. Matsson, EM, Eriksson, UG, Palm, JE, Artursson, P, Karlgren, M, Lazorova, L, Brannstrom, M, Ekdahl, A, Duner, K, Knutson, L, Johansson, S, Schutzer, K-M and Lennernäs, H. Combined in Vitro-in Vivo Approach To Assess the Hepatobiliary Disposition of a Novel Oral Thrombin Inhibitor. *Molecular Pharmaceutics*, 2013, 10 (11), 4252.
10. Matsson, P and Artursson, P. Computational Prospecting for Drug-Transporter Interactions. *Clinical Pharmacology and Therapeutics*, 2013, 94 (1), 30.
11. Neve, EPA, Artursson, P, Ingelman-Sundberg, M and Karlgren, M. An Integrated in Vitro Model for Simultaneous Assessment of Drug Uptake, Metabolism, and Efflux. *Molecular Pharmaceutics*, 2013, 10 (8), 3152.
12. Norinder, U and Boström, H. Representing descriptors derived from multiple conformations as uncertain features for machine learning. *Journal of Molecular Modeling*, 2013, 19 (6), 2679
13. Pedersen, C, Vallhov, H, Engqvist, H, Scheynius, A and Strømme, M. Nanoscale Size Control of Protein Aggregates. *Small*. 2013, 9 (19) 3320-6.
14. Pedersen, JM, Matsson, P, Bergström, CAS, Hoogstraate, J, Norén, A, LeCluyse, EL and Artursson, P. Early Identification of Clinically Relevant Drug Interactions with the Human Bile Salt Export Pump (BSEP; ABCB11). *Toxicological Sciences*, 2013, 136 (2), 328.

15. Persson, LC, Porter, CJH, Charman, WN and Bergström, CAS. Computational Prediction of Drug Solubility in Lipid Based Formulation Excipients. *Pharmaceutical research*, 2013, 30 (12), 3225.
16. Prieto, P, Kinsner-Ovaskainen, A, Stanzel, S, Albella, B, Artursson, P, Campillo, N, Cecchelli, R, Cerrato, L, Diaz, L, Di Consiglio, E, Guerra, A, Gombau, L, Herrera, G, Honegger, P, Landry, C, O'Connor, J E, Paez, JA, Quintas, G, Svensson, R, Turco, L, Zurich, MG, Zurbano, MJ and Kopp-Schneider, A. The value of selected in vitro and in silico methods to predict acute oral toxicity in a regulatory context: Results from the European Project ACuteTox. *Toxicology in Vitro*, 2013, 27 (4), 1357.
17. Tehler, U, Fagerberg, JH, Svensson, R, Larhed, M, Artursson, P and Bergström, Christel AS. Optimizing Solubility and Permeability of a Biopharmaceutics Classification System (BCS) Class 4 Antibiotic Drug Using Lipophilic Fragments Disturbing the Crystal Lattice. *Journal of Medicinal Chemistry*, 2013, 56 (6), 2690.
18. Vodnala, SK, Lundback, T, Sjöberg, B, Svensson, R, Rottenberg, ME and Hammarstrom, LGJ. In Vitro and In Vivo Activities of 2-Aminopyrazines and 2-Aminopyridines in Experimental Models of Human African Trypanosomiasis. *Antimicrobial Agents and Chemotherapy*, 2013, 57 (2), 1012.
19. Vodnala, SK, Lundback, T, Yeheskieli, E, Sjöberg, B, Gustavsson, A-L, Svensson, R, Olivera, GC, Eze, AA, de Koning, HP, Hammarström, LGJ and Rottenberg, ME. Structure-Activity Relationships of Synthetic Cordycepin Analogues as Experimental Therapeutics for African Trypanosomiasis. *Journal of Medicinal Chemistry*, 2013, 56 (24), 9861.
20. Warren, DB, Bergström, CAS, Benameur, H, Porter, CJH and Pouton, CW. Evaluation of the Structural Determinants of Polymeric Precipitation Inhibitors Using Solvent Shift Methods and Principle Component Analysis. *Molecular Pharmaceutics*, 2013, 10 (8), 2823.
21. Öhrvik, H, Tydén, E, Artursson, P, Oskarsson, A and Tallkvist, J. Cadmium Transport in a Model of Neonatal Intestinal Cells Correlates to MRP1 and 2 not DMT1 or FPN1. *ISRN Toxicology*. 2013, Article ID 892364.

Funding

The group (including UDOPP) receives funding from the Swedish Research Council (infrastructure, medical and science branches), the European Research Council, Swedish Governmental Agency for Innovation Systems, European Commission (Innovative medicines Initiative – Orbito and ENABLE, Marie Curie Initial Training Network, Trans-Int), The Swedish Fund for Research without Animal Experiments, The Medical Products Agency, SciLifeLab Nordforsk, OE and Edla Johanssons Scientific Foundation, Magnus Bergvall Foundation, Carl Trygger Foundation, Lars Hierta Memorial Foundation, The Valborg Jacobson Foundation and Industry.

Doctoral Dissertation

Vildhede, A. *In vitro* and *in silico* Predictions of Hepatic Transporter-Mediated Drug Clearance and Drug-Drug Interactions *in vivo*. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 193, 2015

Awards 2015

1. Holmboe M., Fagerberg J.H., Anwar J., Bergström C.A.S. Lipoidal structures present in simulated intestinal fluids modeled by molecular dynamics simulations. PhysChem Forum, Jan 28 - 29, 2015, Uppsala, Sweden. (Best poster award)
2. Vildhede, A. Graduate Student Research Award in Pharmacokinetics, Pharmacodynamics and Drug Metabolism and Clinical Pharmacology and Translational Research by, the American Association of Pharmaceutical Scientists, October 25-29, 2015, Florida, USA.

Arrangement of research seminars and courses 2015

1. Symposium, 6th Symposium on Pharmaceutical Profiling in Drug Discovery and Development, January 28, 2016. Organizers: Per Artursson, Pawel Baranczewski, Christel Bergström and Pär Matsson. See <https://www.scilifelab.se/wp-content/uploads/2014/12/the-flyer.pdf>
2. Forum, PhysChemForum15 meeting, Crossing barriers, Uppsala January 29, 2016. Organizer: Christel Bergström. See <http://physchem.org.uk/symp15/pcf15.htm>
3. Conference, 49th Gattefossé Journées Galéniques de St Rémy de Provence, France, June 24-27, 2015. Organizer: Christel Bergström and Christopher Porter together with the Foundation Gattefossé.
4. Round table discussion, "Lipophilicity in drug development: Too much or not enough?" at the AAPS Annual meeting, Orlando, Florida, Oct 27, 2016. Organizers: Christel Bergström, Mehran Yazdani, Jasmine Musakhanian
5. Short Course: New Cell Based Approaches for Better Predictions of Drug Transport and Cellular Drug Exposure. 20th North American ISSX Meeting. October 18 – October 22, 2015. Orlando, USA. Presenter: Per Artursson
6. Seminar by Dr Ulf Norinder, SweTox. "Conformal Prediction - Predicting with Confidence: Biomedical dataset applications" May 18, 2015. Host: Christel Bergström.
7. Seminar by Dr Erik Eliasson, "Drug-Drug Interactions in Clinical Practice". November 3, 2015. Host: Per Artursson.
8. Seminar by Dr Jacek Wisniewski, "Beyond FASP and the Total Protein Approach" August 27, 2015. Host: Per Artursson.
9. PhD course: Human Cell Culture. Methods and Applications June 1-5, Uppsala

Presentations at symposia and congresses 2015

Abstracts Posters

1. Alhalaweh, A., Bergström, C.A.S., Taylor, L.S. Compromised dissolution properties of multicomponents amorphous formulations. AAPS Annual meeting, October 25-29, 2015, Orlando, USA.
2. Alhalaweh, A., Bergström, C.A.S., Taylor, L.S. Maximum achievable supersaturation and membrane transport of amorphous drug formulations in co-administered with a crystalline drug. Presented as a poster at AAPS Annual meeting, October 25-29, 2015, Orlando, USA.
3. Alskär, LC., Diesch E., Friberg, ASS., Porter, CJH., Bergström, CAS. Prediction of Drug Solubility in Lipid Based Formulations from Molecular Structure. NordForsk FPTP meeting 2015, 21-24 January 2015, Copenhagen, Denmark.
4. Alskär, LC., Porter, JH., Bergström CAS. Tools for Early Prediction of Drug Loading in Lipid-Based Formulations. Gordon Research Conference, Preclinical Form & Formulation for Drug Discovery, Waterville Valley NH United States, 7-12 June, 2015. Waterville Valley in Waterville Valley NH United States.
5. Alskär, LC., Porter, JH., Bergström CAS. Tools for Early Prediction of Drug Loading in Lipid-Based Formulations. AAPS Annual meeting, 25-29 October 2015, Orlando, USA.
6. Andersson, S.B.E., Alvebratt, C., Bergström, C.A.S. Controlled Suspensions as a Method for Small Scale Dissolution Profiling of Poorly Soluble Compounds. PhysChem Forum, January 28 - 29, 2015, Uppsala, Sweden.
7. Andersson, S.B.E., Alvebratt, C., Bergström, C.A.S. Controlled Suspensions as a Method for Small Scale Dissolution Profiling of Poorly Soluble Compounds. OrBiTo Open Science Meeting, July 2, 2015, Paris, France.
8. Andersson, S.B.E., Alvebratt, C., Gråsjö, J., Bergström, C.A.S. Controlled Suspensions as a Method for Small Scale Dissolution Profiling of Poorly Soluble Compounds. 4th World Conference on Physico Chemical Methods in Drug Discovery and Development, September 21 - 24, 2015, Red Island, Croatia.
9. Gaugaz, F. Z., Wiśniewski, J. R. Tryptophan Fluorescence (WF) Measurements for Total Protein and Peptide Assays. The Human Proteome D7 Keystone Symposium. April 24-29, 2015. Stockholm, Sweden. Encore presentation at AAPS, October 25-29, 2015, Orlando, USA.
10. Gaugaz, F., Artursson, P., Wisniewski, J. Fast and Sensitive Total Protein and Peptide Assays for Proteomic Analysis. AAPS, October 25-29, 2015, Orlando, USA.
11. Gaugaz F. Z., Gröer C., Busch D., Oswald S., Wiśniewski J. R., Warpman-Berglund U., Helleday T., Baranczewski P., Artursson P. Proteomic Quantification of Drug Transporters and Metabolizing Enzymes in Cancer Cell Lines. EACR AACR SIC Special Conference: Anticancer drug response and drug resistance, June 20-23, 2015, Florence, Italy. Encore presentation at Biomedical transporters, August 9-13, 2015, Lugano, Switzerland and AAPS, October 25-29, 2015, Orlando, USA.

12. Gaugaz, F., Groer, C., Busch, D., Oswald, S., Wisniewski, J., Warpman Berglund, B. Helleday, T., Baranczewski, P., Artursson, P. Proteomic Quantifications of Drug Transporters, Metabolizing Enzymes and Cancer Target MTH1 in Cancer Cell Lines, AAPS, October 25-29, 2015, Orlando, USA.
13. Holmboe M., Larsson P., Bergström. C.A.S., Drug solubilization in lipoidal nanoaggregates in simulated intestinal fluid, AAPS, October 25-29, 2015, Orlando, USA
14. Lundquist P., Khan, E. Artursson P. Ussing chambers for the study of nanoparticle permeability in the human intestine. Trans-Int yearly meeting, April 26-28, 2015, Barcelona, Spain.
15. Lundquist, P., Khan, E., Webb, D., Hellström, P., Keita, Å., Wiren, M., Söderholm, J., Artursson, P. Ussing Chambers for the Study of Nanoparticle Permeability in the Human Jejunum. AAPS, October 25-29, 2015, Orlando, USA.
16. Mateus, A., Treyer, A., Matsson, P., Karlgren, M., Artursson, P. Impact of Drug Transporters on Intracellular Unbound Drug Concentrations, 20th North American ISSX Meeting, October 18-22, 2015, Orlando, USA.
17. Mateus, A., Treyer, A., Matsson, P., Karlgren, M., Artursson, P. Impact of Drug Transporters on Intracellular Unbound Drug Concentrations, AAPS, October 25-29, 2015, Orlando, USA.
18. Matsson P, Fenu LA, Lundquist P, Wisniewski J, Kansy M, Artursson P. Quantifying the impact of transporters on cellular drug permeability. AAPS/ITC Joint Workshop on Drug Transporters In ADME: From the Bench to the Bedside April 20-22, 2015, Baltimore, USA.
19. Matsson, P., Over, Björn, Tyrchan, C., Artursson, P., Doak, B., Hilgendorf, C., Lee, M. IV, Lewis, R., McCarren, P., Muncipinto, G., Perry, M., Svensson, R., Duvall, J., Kihlberg, J. Expanding Drugable Space by Identifying Rules for Macrocycle ADME. AAPS, October 25-29, 2015, Orlando, USA.
20. Over B, Matsson P, Tyrchan C, Artursson P, Doak BC, Hilgendorf C, Lee MD IV, Lewis R, McCarren P, Muncipinto G, Perry M, Svensson R, Duvall JR, Kihlberg J. Expanding drugable space by identifying rules for macrocycle ADMET. American Association of Pharmaceutical Scientists Annual Meeting, October 25-29 2015, Orlando, USA.
21. Treyer, A., Mateus, A., Matsson, P., Artursson, P. Impact of Intracellular Lipid Stores on Intracellular Drug Exposure. AAPS, October 25-29, 2015, Orlando, USA.
22. Wegler, C., Gaugaz, F., Andersson, T. Wisniewski, J., Busch, D., Oswald, S., Weiss, F., Hammer, H., Joos, T., Poetz, O., van de Steeg, E., Achour, B., Rostami-Hodjegan, A., Artursson, P. Protein Quantification of Human Hepatic Drug Transporters and Metabolizing Enzymes: An Inter-Laboratory and Methodological Comparison. AAPS, October 25-29, 2015, Orlando, USA.
23. Ölander, M., Wisniewski, J., Noren, A., Artursson, P. To Attach or Not to Attach: Factors behind Variable Adhesion Properties of Cryopreserved Human Hepatocytes. AAPS, October 25-29, 2015, Orlando, USA.

24. Ölander, M., Wisniewski, J., Noren, A., Artursson, P. To Attach or Not to Attach: Factors behind Variable Adhesion Properties of Cryopreserved Human Hepatocytes. 20th North American ISSX Meeting, October 18-22, 2015, Orlando, USA.

Abstracts Oral Presentation

1. Artursson, P. Pharmaceutical (ADME) profiling for academic drug discovery scientists. PhysChem Forum 15. January 28, 2015. Uppsala, Sweden.
2. Artursson, P. Transport proteins that determine drug efficacy: in vitro and in vivo correlations. Department seminar series, Division of Clinical Pharmacology, Karolinska Institutet. March 4, 2015. Stockholm, Sweden.
3. Artursson, P. A Proteomics Informed Approach for Integrated Prediction of Drug Uptake, Metabolism and Efflux. Gordon Research Conference 2015. April 26 – May 1, 2015. Lucca (Barga), Italy
4. Artursson, P. The impact of transporters on intestinal drug absorption. Läkemedelsakademins Drug Processing and Delivery 2015. May 6 – May 7, 2015. Uppsala, Sweden
5. Artursson, P. Impact of intracellular unbound drug concentration on target engagement. GSK Meeting. June 8- June 9, 2015. Stevenage, United Kingdom.
6. Artursson, P. Assessing the importance of intracellular unbound concentration measurements for understanding target engagement. ELRIG conference on Advances in Cell-based Screening in Drug Discovery. June 16 – June 17, 2015. Mölndal, Sweden
7. Artursson, P. Intestinal delivery of peptides – extrapolations from studies in freshly isolated human intestine. Merck & Co Inc. Roundtable Meeting October 15- October 16, 2015, Philadelphia, USA.
8. Artursson, P. A proteomics informed approach for integrated prediction of drug uptake, metabolism and efflux. Merck & Co Inc. Roundtable Meeting. October 15-October 16, 2015. Philadelphia, USA.
9. Artursson, P. Qualifying the impact of transporters on cellular (Caco-2) drug permeability. Ron Borchardt Tribute, University of Kansas. October 21 – October 23, 2015. Lawrence, USA.
10. Artursson, P. Translational Models for Prediction of Drug Transport and Cellular Drug Exposure. Drug Transporters Summit-Janssen. November 9-12, 2015. Leiden, Netherlands.
11. Bergström, C.A.S. Computer-based tools identify successful formulation pathways for poorly soluble drugs. 4th Annual meeting on Future Performance Testing of Pharmaceuticals, Jan 22, 2015, Copenhagen, Denmark.
12. Bergström, C.A.S. Computer-based tools identify successful formulation pathways for poorly soluble drugs. 6th Symposium on Pharmaceutical Profiling in Drug Discovery and Development, Jan 28, 2015, Uppsala, Sweden.
13. Bergström, C.A.S. Predictive tools for increased delivery of poorly soluble drugs. Research Seminar at the University of Applied Sciences Northwestern Switzerland, Feb 3, 2015, Basel, Switzerland.

14. Bergström, C.A.S. In silico and in vitro tools to identify formulation pathways for poorly soluble drugs. EDAN meeting, March 16, 2015, Leuven, Belgium.
15. Bergström, C.A.S. Intestinal Lipoidal Nanostructures – A Natural Bridge to Increased Drug Delivery. The Swedish Research Council, Apr 9, 2015, Stockholm, Sweden.
16. Bergström, C.A.S. Oral Delivery of Poorly Soluble Drugs – Impact of Natural and Formulation-Assisted Solubilization. Faculty day, Apr 21, 2015, Uppsala, Sweden.
17. Bergström, C.A.S. Tools to Predict Intestinal Drug Dissolution under Fasted and Fed Conditions. Drug Processing and Delivery, May 6-7, 2015, Uppsala, Sweden.
18. Bergström, C.A.S. It's life Jim but not as we'd like it: navigating beyond rule-of 5 chemical space. 49th Journées de Galenique de St Remy de Provence, Jun 24-26, 2015, St Remy, France.
19. Bergström, C.A.S. Predictive Tools for Delivery of Poorly Soluble Drugs. CRS Nordic Chapter meeting, Jul 25, 2015, Edinburgh, United Kingdom.
20. Bergström, C.A.S. Biopharmaceutical profiling and drug delivery. SenBioTar meeting, Aug 18, 2015, Nottingham, United Kingdom.
21. Bergström, C.A.S. Predictions of solubility and formulation strategies for poorly solubles: in silico and in vitro tools to rationalize the drug development process. Novartis, Sept 1, 2015, Basel, Switzerland.
22. Fagerberg, J. H. Experimental and Computational Predictions of Drug Solubility in Human Gastrointestinal Fluids - Gabi Award Lecture, Drug Processing and Delivery meeting, 6-7 May, 2015, Uppsala, Sweden.
23. Gaugaz, F. Z., Drug Transport and Metabolism in Cancer Cell Lines. 6th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. January 28, 2015. Uppsala, Sweden.
24. Larsson, P., Molecular dynamics simulations, Department Workshop, November 30, Uppsala, Sweden.
25. Lundquist P. Use of isolated hepatocytes for assessing transporter function - Point-counterpoint 2015 AAPS/ITC Workshop on Drug Transporters in ADME: From the Bench to the Bedside, April 20-22, 2015, Baltimore, USA.
26. Lundquist P., Elin K., Artursson P. Ussing chambers for the study of nanoparticle permeability in the human intestine. Trans-Int yearly meeting, April 26-28, 2015, Barcelona, Spain.
27. Lundquist P., Elin K., Artursson P. Ussing chambers for the study of nanoparticle permeability in the human intestine. Drug Processing and Delivery, Läkemedelsakademin, May 7, 2015, Uppsala, Sweden.
28. Matsson, P. Predictions of cellular drug binding and implications for intracellular drug concentrations and effects. International Society for the Study of Xenobiotics 13th European meeting. June, 2015. Glasgow, Scotland.
29. Matsson, P. Modeling drug distribution at the cellular and molecular scales. Swedish Pharmacometrics Association. October, 2015. Stockholm, Sweden.
30. Matsson, P. Preclinical ADME. Research School in Drug Discovery and Development (a joint international graduate school between Uppsala University, Karolinska Institute and Lund University). March, 2015. Uppsala, Sweden.
31. Wegler, C., Gaugaz, F., Andersson, T. Wisniewski, J., Busch, D., Oswald, S., Weiss, F., Hammer, H., Joos, T., Poetz, O., van de Steeg, E., Achour, B., Rostami-Hodjegan, A., Artursson, P. Protein Quantification of Human Hepatic

Drug Transporters and Metabolizing Enzymes: An Inter-Laboratory and Methodological Comparison. AAPS, October 25-29, 2015, Orlando, USA

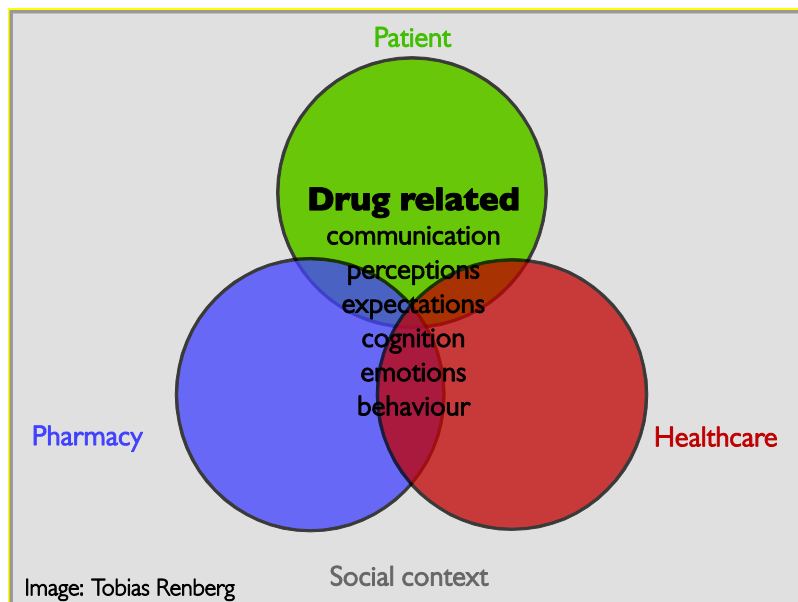
32. Mateus, A. Impact of Intracellular Unbound Drug Concentrations on Target Engagement. VII Spanish Drug Discovery Network meeting (in collaboration with Society for Laboratory Automation and Screening). November 12 – November 13, 2015. Barcelona, Spain.

Pharmacy Practice and Policy

Increasing expenditures for pharmaceuticals and limited health care resources have put focus on the use of medicines. Modern pharmaceuticals are well documented and sophisticated aids, but the final treatment outcome depends on how they are handled in society, by e.g. politicians, prescribers, pharmacists and patients. The overall aim for our research is to contribute to an improved understanding of the role of medicines for individuals and societies. This research is intended to lead to improved use of medicines, to the benefit of individuals and society at large.

We use theories and methodologies from social sciences and apply them on the field of pharmacy. Research questions are related to medicines and/or professions and organizations dealing with medicines. Nearly all projects are run by multidisciplinary research teams involving both internal and external researchers.

Our research deals with pharmacy policy, not least the recent deregulation of the pharmacy market, including sales of non-prescription medicines outside pharmacies. We also study health care professions, predominantly pharmacists. How are the pharmacy professions developing and how are they seen by society at large? Pharmacies and their services is another area for our research, for example we investigate safety and safety culture within pharmacy.



Pharmacy policy

Sofia Kälve mark Sporrong, Kristin Wisell

During the last years the pharmacy market in Sweden has been subject to significant changes, due to deregulation of e.g. pharmacy ownership, sale of non-prescription medicines outside pharmacies and the role of governmental authorities. We look into the ideological arguments behind these changes, as well as how different stakeholders have acted during this period of transformation.

Pharmacies and patient safety

Sofia Kälve mark Sporrong, Annika Nordén Hägg

We target the organizational level of pharmacy practice by investigating the influence of safety cultures on dispensing errors at pharmacies. This is done in order to understand the underlying mechanisms that trigger errors, the reporting of errors and, eventually, to initiate preventive measures. We also study safety issues regarding sales of non-prescription medicines outside pharmacies.

Pharmacy communication

Sofia Kälve mark Sporrong, Erika Olsson

The communication between pharmacy staff and patients with regard to prescription medicines is studied, especially when it comes to content of the dialogue, but also socio-demographic factors are taken into considerations..

Conducting research in pharmacies

Pia Frisk, Sofia Kälve mark Sporrong

When conducting research on experiences and attitudes of medicine users towards their specific treatments, pharmacies are practical for collecting data or including patients in studies. There are, however, methodological problems, e.g. with selection bias. Also, the dispensing process can be affected. In Sweden, short electronic questionnaires have been distributed through pharmacies for some years. Methodological and other aspects of this service are investigated.

Patients' view of research and researchers

Sofia Kälve mark Sporrong, Malin Masterton

Patients are often taking part in research within the medical and pharmaceutical sciences. But how do they look upon their role as test subject, what are their conceptions of the usefulness of research and the underlying interests of researchers?

This is studied in order to make visible power relations and incentives in research on human subjects.

Members of the group during 2015

Charlotta Alvarmo, Lecturer

Pia Frisk, PhD Student

Malin Masterton, Research scientist

Jannike Stenlund, Lecturer

Kristin Wisell, PhD Student

Katarina Öjefors-Stark, Lecturer

Publications, reviews and book chapters 2015

1. Wisell, K., Winblad, U., and Kälve-mark-Sporrong, S. Reregulation of the Swedish pharmacy sector-A qualitative content analysis of the political rationale, *Health Policy* 2015, 119, 648-653.
2. Frisk, P., Bergman, U., and Kälve-mark-Sporrong, S. Exploring community pharmacists' experiences of surveying patients for drug utilization research purposes, *Int. J. Clin. Pharm.* 2015, 37, 522-528.

Publications, reviews and book chapters 2014

3. Frisk, P, Kälve-mark-Sporrong, S and Wettermark, B. Selection bias in pharmacy-based patient surveys. *Pharmacoepidemiology and Drug Safety*, 2014, 23 (2), 128.
4. Martin, A, Godman, B, Miranda, J, Tilstone, J, Saleem, N, Olsson, E, Acosta, A, Restrepo, L and Bennie, M. Measures to improve angiotensin receptor blocker prescribing efficiency in the UK : findings and implications. *Journal of Comparative Effectiveness Research*, 2014, 3 (1), 41.
5. Olsson, E, Ingman, P, Ahmed, B and Kälve-mark-Sporrong, S. Pharmacist-patient communication in Swedish community pharmacies. *Research in Social and Administrative Pharmacy*, 2014, 10 (1), 149.

Publications, reviews and book chapters 2013

1. Tully, MP, Kettis, Å, Höglund, AT, Morlin, C, Schwan, Å and Ljungberg, C. Transfer of data or re-creation of knowledge - Experiences of a shared electronic patient medical records system. *Research in Social and Administrative Pharmacy*, 2013, 9 (6), 965.

2. Wallman, A, Vaudan, C and Kälve mark Sporrong, S. Communications Training in Pharmacy Education, 1995-2010. *American Journal of Pharmaceutical Education*, 2013, 77 (2), 36.
3. Rönnbäck, E, Kälve mark Sporrong, S and Österlund, A. Number of Daily Doses Does not Affect Compliance with Flucloxacillin Prescriptions. *International Journal of Clinical Medicine*. 2013, 4 (9): 384.

Pharmaceutical Physical Chemistry

Professor Martin Malmsten

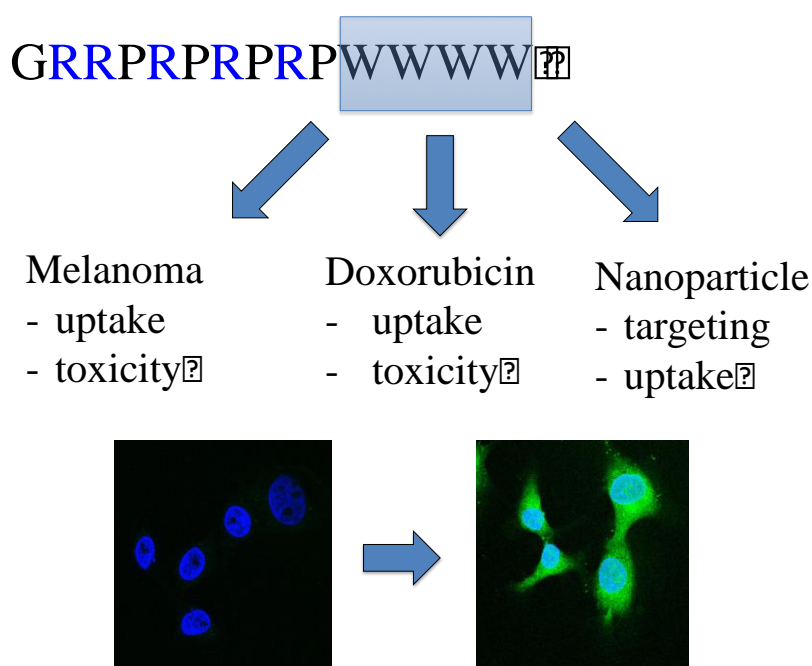
Within the group for Pharmaceutical Physical Chemistry, research is performed on discovery, optimization, and delivery of peptide drugs, with particular focus on antimicrobial, anti-inflammatory and anticancer drugs. The research is characterized by broad collaborations to span the range from basic biophysical and physicochemical investigations, to studies of antimicrobial, anti-inflammatory, and anticancer effects, as well as cell toxicity. The research is based on advanced experimental physicochemical methodology, often combined with theoretical modeling. Areas covered include i) host defense peptides, ii) interactions between microgels and peptides/proteins, iii) modeling of microgel interactions with proteins, peptides, surfactants and amphiphilic drugs, iv) protein sorting in polyelectrolyte networks, v) nanoparticulate drug delivery systems, and vi) lipoprotein interactions with lipid membranes in atherosclerosis.

Project area 1: Host defense peptides

Prof Martin Malmsten, Shalini Singh, Lise-Britt Wahlberg

As one of the main focus areas we investigate biological as well as biophysical properties of antimicrobial and anti-inflammatory peptides. Due to growing problems with multidrug resistance, there is an increasing need to find new types of antibiotics, which has prompted an increased interest in such peptides. Through structure-activity relationship studies, we have identified a number of peptides, e.g., from the complement and coagulation systems, which display potent antimicrobial and/or antiinflammatory effect, but simultaneously low toxicity. With these peptides, we investigate effects of single amino acid modifications to further improve efficiency and selectivity. The research involves parallel studies on antibacterial and antiinflammatory effects, cytotoxicity, and biophysical mechanistic phenomena on model lipid systems (vesicles, supported mono- and bilayers). Apart from results from our research being published in high profile journals, this has resulted in a number of patent applications, and in the development of some of these peptides towards therapeutic applications through two start-up companies. One of these peptides has successfully undergone two Phase I/IIa clinical trials. Exemplifying activities during 2015, lipid membrane and lipopolysaccharide (LPS) interactions were investigated for a series of amphiphilic and cationic peptides derived from human heparin cofactor II, using dual polarization interferometry, ellipsometry, circular dichroism (CD), cryoTEM, and z-potential measurements. Antimicrobial effects of these peptides were compared to their ability to disorder bacterial lipid membranes, while their capacity to block endotoxic effects of LPS was correlated to the binding of these peptides to LPS and its lipid A moiety, and to charge, secondary structure, and morphology of peptide/LPS complexes. In particular, fragmentation and densification of LPS aggregates correlate to the anti-endotoxic effect of these peptides, thus identifying peptide-induced packing transitions in LPS aggregates as key for anti-endotoxic functionality. PEGylation of these peptides reduces peptide binding to lipid membranes, an effect accentuated at increasing PEG length but less sensitive to conjugation site. The reduced binding causes suppressed

liposome leakage induction, as well as bacterial lysis. As a result of this, the antimicrobial effects of KYE28 is partially lost with increasing PEG length, but hemolysis also strongly suppressed and selectivity improved. Through this, conditions can be found, at which the PEGylated peptide displays simultaneously efficient antimicrobial effects and low hemolysis in blood. Importantly, PEGylation does not markedly affect the anti-inflammatory effects of these peptides. The combination of reduced toxicity, increased selectivity, and retained anti-inflammatory effect after PEGylation, as well as reduced scavenging by serum proteins, thus shows that PEG conjugation may offer opportunities in the development of effective and selective anti-inflammatory peptides. Recently, we extended our studies of peptide-membrane interactions to studies of anti-cancer effects of antimicrobial peptides. In particular, W-tagging of such peptides was demonstrated to provide a tool for increasing selective peptide internalization in melanoma cells, resulting in toxicity against these, but not against the non-malignant cells. From a combination of biophysical studies on membrane binding/destabilization and biological studies on cell uptake and toxicity, these effects were shown to be due to increased peptide adsorption to the outer membrane in melanoma cells, caused by the presence of anionic lipids such as phosphatidylserine and ganglioside GM1, and to peptide effects on mitochondria membranes and resulting apoptosis. In addition, such W-tagged peptides could be used for achieving targeted uptake of nanoparticles/drug carriers in melanoma, as well as for facilitating uptake of the low Mw anticancer drug doxorubicin.

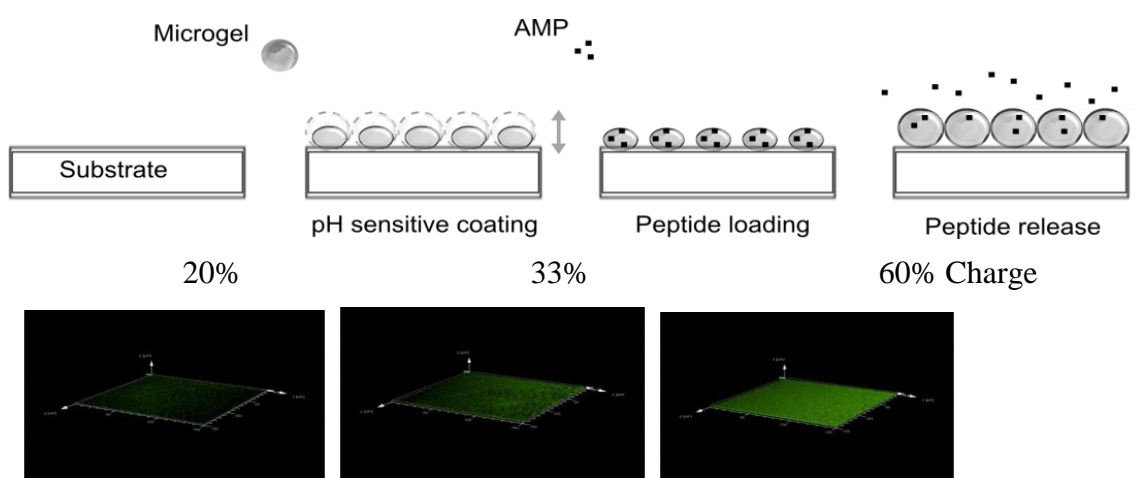


W-tagging of arginine-rich peptides offers a way to reach selective uptake into, and toxicity against, melanoma cells over non-malignant cells, such as fibroblasts, keratinocytes, and erythrocytes. Such peptides can also be used to reach selective targeting of melanoma cells for nanoparticulate drug delivery systems, and also facilitates cell uptake on low molecular weight anti-cancer drugs such as doxorubicin.

Project area 2: Interaction between microgels and proteins/peptides

Prof Martin Malmsten, Prof Per Hansson, Dr Yanling Cai, Ronja Widenbring, Lina Nyström, Randi Nordström, Jonas Gernandt

In this project area we investigate microgels and nanogels as delivery systems for proteins and peptide drugs, including effects of peptide/protein-microgel interactions and of transport restrictions within the gel network, as well as effects on the loading/release and polypeptide distribution within the gel particles. During the last couple of years, focus has been placed on factors determining proteolytic degradation of peptides loaded into microgel carriers, but also on how peptide/protein load in microgels affect biodegradation of the microgel matrix. Much of this work is based on a method combination of micromanipulator-assisted light microscopy, confocal microscopy, circular dichroism, and fluorescence spectroscopy, and experimental work is generally coupled also to theoretical modelling. In addition, we also initiated two PhD projects during the last two years, one aiming at microgels as delivery systems for antimicrobial and anti-inflammatory peptide drugs (funded by EU) and one directed at microgel-based surface coatings of implants for controlled host response (funded by the Swedish Research Council). The latter projects have included methodological development, e.g., in terms of AFM investigations of both topological and mechanical properties of highly swollen microgels *in situ*, as well as confocal microscopy approaches for probing peptide loading and release from such microgel coatings. This work has furthermore included the development/implementation of new chemistries for microgel synthesis and surface coupling. In the context of microgels as carriers for antimicrobial and anti-inflammatory peptides, key developments furthermore include the application of novel biological methodology for investigation delivery system performance, including different biofilm models and models of intracellular bacteria infections (notably tuberculosis). With this battery of novel approaches, we have already obtained a series of promising results, and expect them to enable powerful progression in these areas the coming years.

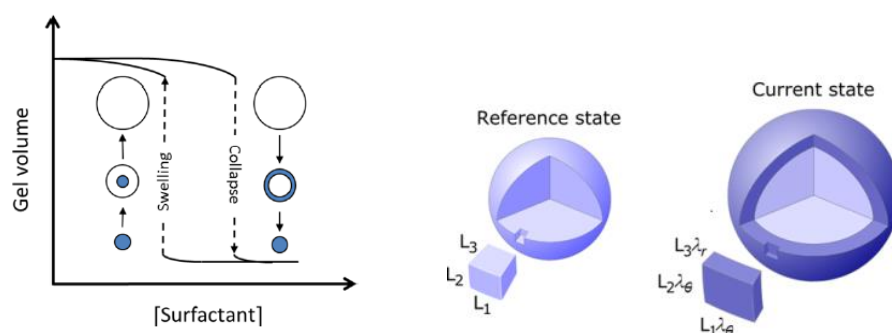


Schematic illustration of microgel coating of biomaterials, as well as subsequent peptide loading (top). Shown also (bottom) are confocal microscopy images with labeled peptide loaded to surface-bound microgels of different charge density.

Project area 3: Modelling of microgel interactions with proteins, peptides, and surfactants

Prof Per Hansson, Jonas Gernandt, Prof Martin Malmsten

Supporting our experimental activities on microgels as protein and peptide drug delivery systems, research in this area focuses on generic aspects of the interaction between macroions and polyions. The investigations are focused primarily on electrostatic and elastic effects in systems where proteins, peptides, and surfactant micelles form complexes with cross-linked polyion networks, but complexes in the absence of crosslinks are also investigated. A central problem addressed is the influence of electrostatic and elastic interactions on the distribution of macroions in microgels, in particular in relation to phase coexistence and discrete volume transitions. This is important for understanding binding/release mechanisms, protein sorting and encapsulation in microgels. Working mainly with analytical methods we have developed a molecular thermodynamic model, which, in combination with an elastic field theory, allows for detailed modeling of the propagation of elastic forces in the inhomogeneous and anisotropic network states of core/shell gels. Recently we have successfully modeled the interaction between charged spherical polymer networks and oppositely charged proteins, peptides and surfactant micelles. The results clarify the role of protein/peptide and polyion charge densities, protein/peptide size, cross-linking density and the concentration of added salt.



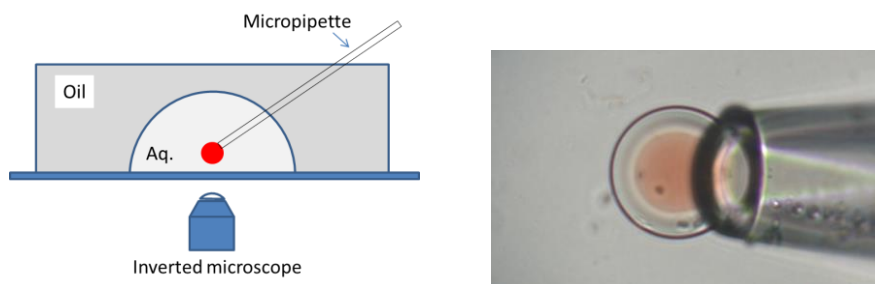
Schematic illustration of the surfactant-induced volume phase transition with hysteresis (left) and the deformation of volume elements in microgels displaying core-shell phase separation.

Project area 4: Protein sorting in polyelectrolyte networks

Prof Per Hansson, Claes Jidheden

In this project we investigate how the interaction between two different water-soluble proteins is affected by the presence of a polyelectrolyte of opposite charge, with special focus on segregation or proteins confined to the same polyelectrolyte network. By investigating the importance of the charge density of proteins and polyelectrolyte and other factors affecting the strength of electrostatic interactions the aim is to clarify to what extent electrostatic interactions mediated by polyelectrolytes is responsible for segregation of two different proteins. We have discovered that the cationic protein

cytochrome c and a protein model (cationic/non-ionic mixed micelles) segregate in negatively charged polyelectrolyte networks to form different domains (core/shell). Two ‘sorting’ mechanisms have been observed and related to the relative strength of the polyelectrolyte-mediated between the proteins/protein models. Another objective is to clarify to what extent intrinsic (short range) attractions lead to segregation. The processes are investigated in small liquid compartments by means of microscopy techniques, assisted by micromanipulators. The problems addressed are relevant for encapsulation of two proteins in microgels for protein drug delivery, and for understanding protein sorting in the secretory machinery of living cells.



Schematic illustration of set-up for microscopy studies of microgels in small liquid compartments (left) and core-shell segregation of cytochrome c (red) and tetradecyl betainate micelles in poly(acrylate-co-acrylamide) microgel.

Project area 5: Nanoparticulate drug delivery systems

Prof Martin Malmsten, Stefano Colombo, Sara Malekhaat Häffner, Lise-Britt Wahlberg

During 2015, we continued our work to develop a versatile platform methodology for improving dissolution kinetics, gastrointestinal absorption, and bioavailability of protein kinase inhibitors (PKIs). The approach is based on dissolving the PKI in an organic solvent together with a matrix-forming polymer, followed by nanoparticle precipitation by sub- or supercritical CO₂. Surfactants added after nanoparticle generation were found to be important for optimal PKI dissolution rate. Focusing on nilotinib, selected formulations were investigated by X-ray diffraction, modulated differential scanning calorimetry, vapor sorption measurements, and electron microscopy. The hybrid nanoparticles were demonstrated to consist of amorphous PKI embedded in a polymer matrix, displaying retained amorphicity also after 12 months of storage. Consequently, nilotinib release rate was dramatically increased in both simulated gastric fluid and simulated intestinal fluid. Similar results indicated flexibility of the approach regarding polymer identity, drug load, and choice of surfactant/copolymer. The translation of the increased dissolution rate found *in vitro* into improved GI absorption and bioavailability *in vivo* was demonstrated for male beagle dogs following oral administration of gelatin capsules containing the hybrid nanoparticles, where a 730% increase in the AUC_{0-24hr} was observed compared to the benchmark formulation. In two follow-up activities, it has been demonstrated that comparable biological effects in dogs can be obtained with this formulation approach also for a number of other PKIs. In addition, the physicochemical mechanisms underlying the beneficial effects have been further clarified.

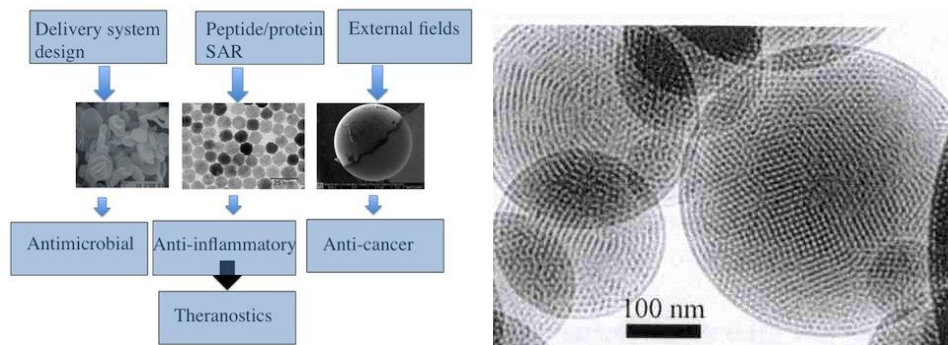


Figure 3. (Left) Inorganic nanoparticles offer wide opportunities as delivery systems for peptide and protein drugs. Through nanoparticle design, drug loading and release can be controlled, while the combination of such systems with external fields (light, NIR, magnetic, ultrasound) allow externally and even remotely triggered drug release, as well as theranostic applications, in which the same system is used for drug delivery and monitoring therapeutic outcome of the treatment. (Right) Mesoporous silica loaded with AMPs displays potent antimicrobial effects combined with low toxicity, of interest, e.g., for delivery systems for treatment of intracellular infections and as biomaterials surface coatings for reducing implant-associated infections .

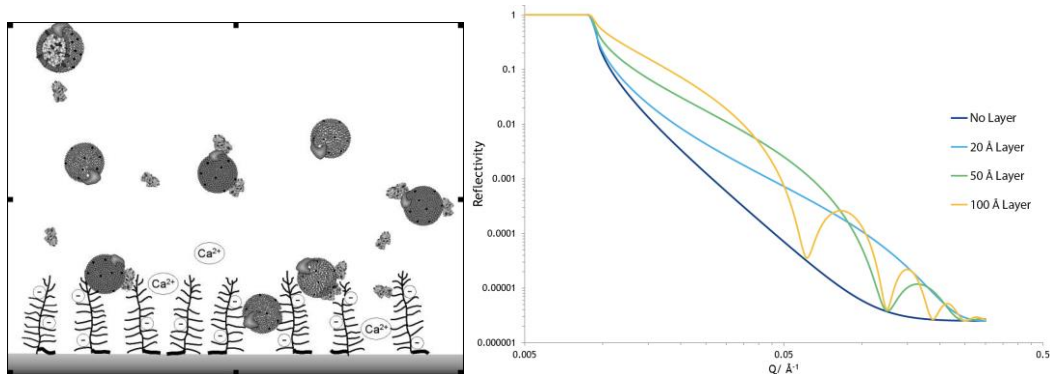
In a second line of research, investigate inorganic nanoparticles as delivery systems for antimicrobial, anti-inflammatory, and anti-cancer peptides. The research activities include delivery system characterization and studies on delivery system interactions with model lipid membranes, but also on biological effects of such carrier systems. Here, we are currently focusing on several project addressing different aspects of nanoparticle-membrane interactions, as well as their use as delivery systems for biomacromolecular drugs, i.e., effects of i) nanoparticle size, charge density, and van der Waals interactions (solid and mesoporous silica particles), ii) particle amphiphilicity (Janus particles), iii) internal particle structure (layered double hydroxides), iv) externally triggerable local heating (magnetic iron oxide nanoparticles), and v) photoactivation and resulting effects on membrane oxidation and stability (TiO₂ nanoparticles). Throughout, we employ a series of lipid membrane models previously established in our work on membrane interactions of amphiphilic peptides, demonstrated to provide biologically relevant information, as well as insight into effects of membrane composition.

Project area 6: Lipoprotein interactions with lipid membranes in atherosclerosis

Prof Martin Malmsten, Kathryn Browning, Prof Günter Siegel

In this project area, focus is placed on the interfacial behaviour of lipoproteins in atherosclerosis and related indication. In doing so, we investigate the deposition of various lipoproteins from clinical patient samples at model proteoglycan-modified surfaces, correlating this to clinical results on atherosclerotic risk factors and effects of drugs in patient groups. While simplistic, this approach has been demonstrated to have potential for evaluating candidate drugs, assessing therapies, and monitoring atherosclerotic risk, as we have been able to demonstrate good correlation between the model system results and clinical observations, e.g., regarding lipoprotein composition and oxidation state, as well as different treatment regimes, for atherosclerosis in

diabetes type II patients, as well as secondary atherosclerosis in by-pass operation patients, using drugs of both synthetic and natural origin. During the last year, we have also deepened our investigations of the interplay between lipoprotein binding to membranes and lipid exchange, as well as between different lipoprotein fractions, in an effort to clarify the role of lipid exchange in atherosclerosis. Such studies are particularly well suited for neutron reflectometry and neutron scattering, since selective deuteration allows individual components to be visualized in complex mixtures with extremely good special resolution. In order to maximize the output of this research, we have recruited a postdoc (Dr. Kathryn Browning), who is responsible not only for this project, but also for ensuring that also other projects in th group are given good support in order to ensure that also these can benefit from the opportunities provided by large-scale facilities, notable neutron sources.



Through two strategic recruitments during 2015, we have invested in a capacity to perform neutron reflectometry and neutron scattering investigations. Such measurements are powerful tools in the investigations of soft matter, including lipid membranes, nanogels, and various other nanoparticles, also in a biological context, since selective deuteration allows individual components to be visualized in complex mixtures with extremely good special resolution. Within the area of lipoprotein-membrane interactions in atherosclerosis, these experimental tools allow studies of lipid exchange, e.g., between lipoproteins and lipid membranes, and between different lipoproteins.

Members of the group during 2015

Martin Malmsten, Professor

Stefano Colombo, Researcher

Yanling Cai, Researcher

Magnus Bergström, Senior lecturer

Kathryn Browning, Researcher

Per Hansson, Professor

Jonas Gernandt, PhD, Senior lecturer

Claes Jidheden, PhD Student

Sara Malekkhaiat Häffner, PhD Student

Randi Nordström, PhD Student
Lina Nyström, PhD Student
Günter Siegel, Visiting professor
Shalini Singh, PhD Student
Lise-Britt Wahlberg, Technician
Ronja Widenbring, PhD Student

Publications, reviews and book chapters 2015

1. Gernandt, J., Hansson, P. Hysteresis in the surfactant-induced volume transition of hydrogels. *Journal of Physical Chemistry B*, 2015, 19, 1717.
2. Bračič, M., Hansson, P., Pérez, L., Zemljič, L. F., Kogej, K. Interaction of sodium hyaluronate with a biocompatible cationic surfactant from lysine: A binding study. *Langmuir*, 2015, 31, 21043.
3. F.C. Hansen, M. Kalle-Brune, M.J.A. van der Plas, A.-C. Strömdahl, M. Malmsten, M. Mörgelin, and A. Schmidtchen, Responses through Interactions with Lipopolysaccharide and Macrophages/Monocytes. *J. Immunol.* 2015, 194, 5397.
4. G. Siegel, G. Meyer-Rath, E. Ermiliov, M. Rodriguez, M. Malmsten, P. Claesson, R. Saunders, R. Hertzner and B. Lindman, Flow Sensing in the Cardiovascular System. *Colloids Surf. A* 2015, 480, 318.
5. M. Malmsten, Protein and Peptide Interactions with Phospholipid Membranes and Surfaces. in *Thin Film Coatings for Biomaterials and Biomedical Applications*. Ed. H. Griesser. Woodhead Publishing, London, 2015.
6. A. Schmidtchen and M. Malmsten, (Lipo)polysaccharide Interactions of Antimicrobial Peptides. *J. Colloid Interface Sci.* 2015, 449, 136.
7. S. Colombo, M. Brisander, J. Haflöf, P. Sjövall, P. Andersson, J. Østergaard, and M. Malmsten, Matrix Effects in Nilotinib Formulations with pH-Responsive Polymer Produced by Carbon Dioxide-Mediated Precipitation. *Int. J. Pharm.* 2015, 494, 205.
8. M. Malmsten, Interactions of Antimicrobial Peptides with Bacterial Membranes and Membrane Components. *Curr. Topic. Med. Chem.* 2015, 16, 16.

Publications, reviews and book chapters 2014

1. Cicuendez, M, Malmsten, M, Carlos Doadrio, J, Teresa Portoles, M, Izquierdo-Barba, I and Vallet-Regi, M. Tailoring hierarchical meso- macroporous 3D scaffolds : from nano to macro. *Journal of Materials Chemistry B*, 2014, 2 (1), 49.
2. Hansen, F, Kalle, M, van der Plas, MJ, Stromdahl, A, Malmsten, M and Schmidtchen, A. The thrombin-derived peptide GKY25 modulates endotoxin-

induced responses through direct interactions with macrophages and monocytes. *Journal of Investigative Dermatology*, 2014, 134, S81.

3. Jesson, G, Brisander, M, Andersson, P, Demirbucker, M, Derand, H, Lennernäs, H and Malmsten, M. Carbon Dioxide-Mediated Generation of Hybrid Nanoparticles for Improved Bioavailability of Protein Kinase Inhibitors. *Pharmaceutical research*, 2014, 31 (3), 694.
4. Kalle, M, Papareddy, P, Kasetty, G, van der Plas, MJA, Morgelin, M, Malmsten, M and Schmidtchen, A. A Peptide of Heparin Cofactor II Inhibits Endotoxin-Mediated Shock and Invasive *Pseudomonas aeruginosa* Infection. *PLoS ONE*, 2014, 9 (7), e102577.
5. Malmsten, M. Antimicrobial peptides. *Uppsala Journal of Medical Sciences*, 2014, 119 (2), 199.
6. Papareddy, P, Kalle, M, Bhongir, RKV, Moergelin, M, Malmsten, M and Schmidtchen, A. Antimicrobial Effects of Helix D-derived Peptides of Human Antithrombin III. *Journal of Biological Chemistry*, 2014, 289 (43), 29790.
7. Papareddy, P, Kalle, M, Singh, S, Morgelin, M, Schmidtchen, A and Malmsten, M. An antimicrobial helix A-derived peptide of heparin cofactor II blocks endotoxin responses in vivo. *Biochimica et Biophysica Acta – Biomembranes*, 2014, 1838 (5), 1225.
8. Schmidtchen, A, Pasupuleti, M and Malmsten, M. Effect of hydrophobic modifications in antimicrobial peptides. *Advances in Colloid and Interface Science*, 2014, 205, 265.
9. Siegel, G, Ermilov, E, Knes, O and Rodriguez, M. Combined lowering of low grade systemic inflammation and insulin resistance in metabolic syndrome patients treated with *Ginkgo biloba*. *Atherosclerosis*, 2014, 237 (2), 584.
10. Siegel, G, Ermilov, E, Pries, AR, Winkler, K, Schmidt, A, Ringstad, L, Malmsten, M and Lindman, B. The significance of lipid peroxidation in cardiovascular disease. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, 2014, 442, 173.
11. Siegel, G, Malmsten, M and Ermilov, E. Anionic biopolyelectrolytes of the syndecan/perlecan superfamily : Physicochemical properties and medical significance. *Advances in Colloid and Interface Science*, 2014, 205, 275.
12. Singh, S, Papareddy, P, Kalle, M, Schmidtchen, A and Malmsten, M. Effects of linear amphiphilicity on membrane interactions of C-terminal thrombin peptides. *RSC Advances*, 2014, 4 (71), 37582.
13. Singh, S, Papareddy, P, Morgelin, M, Schmidtchen, A and Malmsten, M. Effects of PEGylation on Membrane and Lipopolysaccharide Interactions of Host Defense Peptides. *Biomacromolecules*, 2014, 15 (4), 1337.
14. Widenbring, R, Frenning, G and Malmsten, M. Chain and Pore-Blocking Effects on Matrix Degradation in Protein-Loaded Microgels. *Biomacromolecules*, 2014, 15 (10), 3671.

Publications, reviews and book chapters 2013

1. Kalle, M, Papareddy, P, Kasetty, G, Tollefsen, DM, Malmsten, M, Morgelin, M and Schmidtchen, A. Proteolytic Activation Transforms Heparin Cofactor II into a Host Defense Molecule. *Journal of Immunology*, 2013, 190 (12), 6303.
2. Malmsten, M. Inorganic nanomaterials as delivery systems for proteins, peptides, DNA, and siRNA. *Current Opinion in Colloid & Interface Science*, 2013, 18 (5), 468.
3. Månsson, R, Frenning, G and Malmsten, M. Factors Affecting Enzymatic Degradation of Microgel-Bound Peptides. *Biomacromolecules*, 2013, 14 (7), 2317.
4. Schmidtchen, A and Malmsten, M. Peptide interactions with bacterial lipopolysaccharides. *Current Opinion in Colloid & Interface Science*, 2013, 18 (5), 381.
5. Singh, S, Kalle, M, Papareddy, P, Schmidtchen, A and Malmsten, M. Lipopolysaccharide Interactions of C-Terminal Peptides from Human Thrombin. *Biomacromolecules*, 2013, 14 (5), 1482.
6. Singh, S, Papareddy, P, Kalle, M, Schmidtchen, A and Malmsten, M. Importance of lipopolysaccharide aggregate disruption for the anti-endotoxic effects of heparin cofactor II peptides. *Biochimica et Biophysica Acta – Biomembranes*, 2013, 1828 (11), 2709.
7. Papareddy, P, Kalle, M, Sørensen, OE, Malmsten, M, Mörgelin, M, and Schmidtchen, A. The TFPI-2 derived peptide EDC34 improves outcome of Gram-negative sepsis. *PLoS Pathogens* 2013, 9, 1003803.

Funding

The group receives funding from the Swedish Research Council, EU, and Industry.

Doctoral dissertation

Ronja Månsson, University of Uppsala, March 2015, “ Microgel interactions with peptides and proteins – Consequences of peptide and microgel properties”.

Presentations at symposia and congresses 2015

1. Hansson, P., Gernandt, J. Hysteresis in the surfactant-induced volume transition of polyelectrolyte gels. International Workshop on Polyelectrolytes in Chemistry, Biology and Technology. Singapore 26-28 January, 2015. Oral presentation.
2. Malmsten, M. Interactions of antimicrobial peptides with bacterial membranes and membrane components. University of Basel, May 20. Invited lecture.

3. Malmsten, M. Membrane and lipopolysaccharide interactions of antimicrobial and anti-inflammatory peptides. 15th Conference of the International Colloid and Interface Society. Mainz 24-29 May. Keynote lecture.
4. Nyström, L. Malmsten, M. Surface-bound microgels as (antimicrobial) peptide-containing surface coatings. 29th Conference of the European Colloid and Interface Society. Bordeaux 6-11 September. Keynote lecture.
5. Nyström, L., Nordström, R., Bramhill, J., Àlvares-Asencio, R., Saunders, B.R., Rutland, M. and Malmsten, M. Peptide loaded microgels as antimicrobial surface coatings. NordForsk, Copenhagen, 21-23 January, 2015. Oral presentation
6. Nyström, L., Nordström, R., Bramhill, J., Àlvares-Asencio, R., Saunders, B.R., Rutland, M. and Malmsten, M. Peptide loaded microgels as antimicrobial surface coatings. Drug Processing and Delivery, Uppsala, 6-7 May, 2015. Oral presentation
7. Nyström, L., Nordström, R., Bramhill, J., Àlvares-Asencio, R., Saunders, B.R., Rutland, M. and Malmsten, M. Peptide loaded microgels as antimicrobial surface coatings. ULLA summer school, Paris, 4-11 July, 2015. Poster
8. Nyström, L., Nordström, R., Bramhill, J., Àlvares-Asencio, R., Saunders, B.R., Rutland, M. and Malmsten, M. Peptide loaded microgels as antimicrobial surface coatings. ACS, Boston, 16-20 August, 2015. Oral presentation
9. Nyström, L., Nordström, R., Bramhill, J., Àlvares-Asencio, R., Saunders, B.R., Rutland, M. and Malmsten, M. Factors affecting peptide interactions with surface-bound microgels. ASMCS, Uppsala, 4-6 November, 2015. Poster
10. Jidheden, C., Hansson, P. Single microgels in core/shell equilibrium: A novel method for limited volume studies. ASMCS, Uppsala, 4-6 November, 2015. Poster
11. Nordström, R., Nyström, L., Saunders, B.R. and Malmsten, M. pH responsive nanogels as carriers for antimicrobial peptides, Drug processing and delivery 2015 (Läkemedelsakademin), Uppsala, 5-6 May, 2015. Invited lecture.

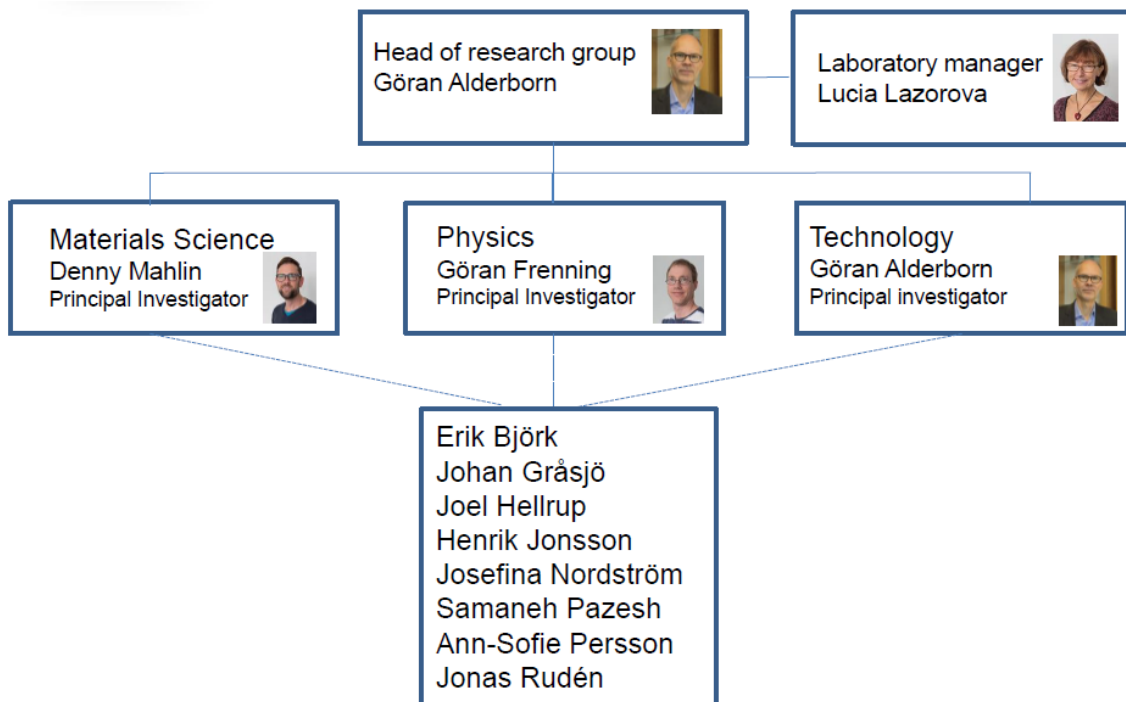
Pharmaceutics - Pharmaceutical formulation and manufacturing science

Professor Göran Alderborn

In the academic discipline Pharmaceutics, the administration, formulation and manufacturing of medicines are treated. The research group in Pharmaceutics at Uppsala University has the mission to deliver fundamental pharmaceutical research that can be translated into better and more cost-effective medicines that will improve health care to the benefit of individuals and society. Our ambition is to conduct pharmaceutical fundamental research that promptly can be translated into the development and manufacturing of effective and safe medicines.

The study of solid systems, their formulation and manufacturing dominates the research of the group with the overall aim to develop new and improved methods and strategies to predict and manipulate the properties of particles and particle systems. In addition, the group conduct research on new drug delivery solutions for controlled drug release.

The group is organized in three project groups, each led by a principle investigator, as shown in the following scheme:



In the Table below, an overview of the research programme of the group, including the projects run within the respective project group, are given and the programme is subsequently briefly described.

Overview of research programme and projects 2015

Project group	Projects
Materials science	<ul style="list-style-type: none"> ▪ Amorphous composites ▪ Dissolution and storage stability predictions of amorphous drugs
Physics	<ul style="list-style-type: none"> ▪ Experimental studies of single particles under confined conditions ▪ Mechanistic models for the interaction between particles under confined conditions ▪ Distinct-particle simulations of confined compression
Technology	<ul style="list-style-type: none"> ▪ Analytical powder compression ▪ Compaction of granular solids ▪ Process induced disordering

Materials science

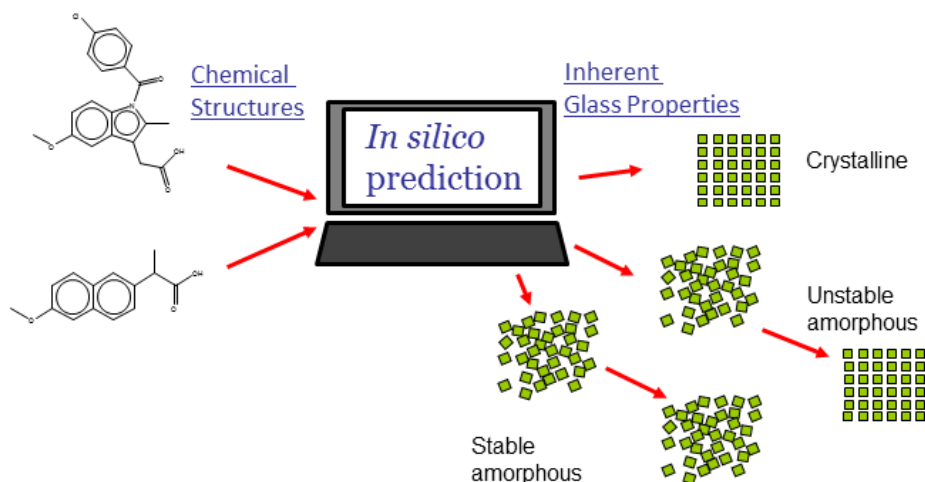
Principal investigator: Denny Mahlin

The physical properties of materials are to a high extent influenced by its solid state. For instance, poorly soluble drugs may attain higher dissolution rate if made amorphous, i.e. transformed into a disordered, non-crystalline state. The mechanical properties, such as elasticity and hardness, of many excipients are also a function of the degree of molecular disorder. Characterization, prediction and control of the solid state of drugs and excipients are hence crucial components of pharmaceutical technology and drug formulation.

During 2015, the following projects have been running within the group:

(a) Properties of amorphous composites

Composites are formed by incorporation of nano-particles into spray-dried powders. The incorporated particles can give the solid advantageous properties, e.g. improved stability of an amorphous compound. We produce and utilize amorphous composites as model to find out how inclusion of various material components affects the properties of the amorphous state. Our focus is to incorporate micro- to nano-sized filler particles into spray-dried amorphous disaccharides and to find out how this affects the material properties and solid-state transformations of the formed composite in terms of crystallization, particle agglomeration behaviour and mechanical properties.



(b) Dissolution and storage stability predictions of amorphous drugs

Amorphization leads to significant changes in material properties and can thus be used to modify pharmaceutical solids to improve their functional properties. By statistical modeling we are developing prediction tools, which give us the opportunity to predict properties of amorphized drug compounds. Glass transition and physical stability are important to evaluate, both when used in the dry state and in aqueous dispersions. Also a better understanding of how these relate to storage stability and dissolution behaviour is in focus. The overall aim is to better understand the molecular properties that govern the ability of a solid material to become a more stable and functional amorphous solid.

Physics

Principal investigator: Göran Frenning

Research in pharmaceutical physics focuses on the behaviour of powders and granular materials, especially under confined conditions, as during manufacturing of tablets. Our ambition is to develop mechanistic models and simulation tools that will enable knowledge at the particle level to be translated into a refined understanding of manufacturing processes ensuring a high quality of the final product. Current work ranges from the development of new test equipment for single particles and formulation of suitable models for particle interactions to full-scale distinct-particle simulations and experimental evaluations of their predictions.

During 2015, the following projects have been running within the group:

(a) Experimental studies of single particles under confined conditions

An improved apparatus for confined triaxial testing of single particles was developed. The apparatus utilises a design in which the particle is confined in a rectangular box whose side-lengths can be varied independently of one another. Hence, the response of individual particles to multiple simultaneous contacts can be determined. This

apparatus will enable a detailed study of the mechanical response of individual particles under confined conditions, an area where the current knowledge is limited.

(b) Mechanistic models for the interaction between particles under confined conditions

The vast majority of the currently used contact models are based on the assumptions of small deformations and independent contacts. These assumptions are not realistic during the later stages of tablet manufacturing by confined powder compression. We are currently developing models for the behaviour of plastically deforming spherical particles under confined conditions, utilising finite-element simulations for model validation. To enforce the constraint imposed by plastic incompressibility, the local relative density, as obtained from Voronoi cells, is used.

(c) Distinct-particle simulations of confined compression

The Discrete Element Method (DEM) is used to translate the understanding at the particle level, as formulated in the mentioned contact models for confined conditions, to the powder bed and tablet. The predictive ability of the models is tested against experimental data for mm-sized granules of various types.

Technology

Principal investigator: Göran Alderborn

The technology of solid dosage forms technology has been an important research direction of the group for more than 20 years and a core topic within this project area is particle science and technology. Based on our knowledge on the compression and compaction of powders, we will continue to investigate powder compression and intend to develop the field analytical powder compression. Moreover, we will continue our ambition to develop a theoretical framework for the properties of granular solids with a special reference to powder compaction. Our project on the properties of amorphous particles will also continue with a focus on the amorphisation of particles during powder flow.

During 2015, the following projects have been running within the group:

(a) Analytical powder compression

Powder compression is a common operation in the manufacturing of pharmaceuticals but also several other types of chemical products. Studies on powder compression and compaction have been conducted for several years within the group. We are now investigating the possibility to use traditional compression parameters as a means to classify powders into groups dependent on their compression behavior and particle mechanics. The overall ambition is to develop a protocol for the characterization of mechanical properties of particles based on powder compression analysis. In addition, we have also the ambition to derive an approach to predict the compactibility of powders based on powder compression analysis.

(b) Compaction of granular solids

Fine particles are often transformed into larger particles, possessing improved physical and technical properties, by granulation. Granular solids are normally clusters of fine particles, characterized on the meso-scale by porosity or solid fraction and on the micro-scale by a complex structure. The granule structure will have a profound effect on the formulation and processing properties of the granules and the understanding of the relationship between granule formation process, granule physical structure and granule processing properties (process-structure-property relationships) for granular solids is an issue of emerging importance. The understanding of such relationships for granular solid needs to be developed in order to firstly, identify and establish strategies for the engineering of granules and, secondly, develop mechanistically based manufacturing control tools.

(c) Process induced disordering

It is today well established that a particulate solid may undergo a transformation from a crystalline to a disordered state during mechanical processing involving breakage of particles, i.e. milling and compaction. However, it is also proposed that particle failure by deformation and friction due to particle sliding may cause such a disordering. Thus, also powder handling involving stresses that will not break particles, such as powder flow, may disorder the particles, causing alterations in the chemical and physical properties of the solid. We intend to investigate the disordering of particles during powder flow and milling and the type of inter-particulate contact processes that may cause disordering. Furthermore, we wish to identify the mechanism on the molecular scale that is involved in the disordering of a solid during powder flow.

Members of the group during 2015

Göran Alderborn, Professor

Erik Björk, Senior lecturer

Göran Frenning, Professor

Johan Gråsjö, Research engineer

Henrik Jonsson, PhD Student

Christin Magnusson, Lecturer

Denny Mahlin, Associate professor

Lucia Lazorova, Research assistant

Josefina Nordström, Research scientist

Mina Heidarian, PhD Student

Joel Hellrup, PhD Student

Samaneh Pazesh, PhD Student

Ann-Sofie Persson, Research scientist

Publications, reviews and book chapters 2015

1. Alhalaweh, A, Alzghoul, A, Mahlin, D and Bergström, CAS. Physical stability of drugs after storage above and below the glass transition temperature: Relationship to glass-forming ability, *International Journal of Pharmaceutics*, 2015, 495 (1), 312.
2. Frenning G. Towards a mechanistic contact model for elastoplastic particles at high relative densities. *Finite Elem. Anal. Des.* 104:56–60, 2015.
3. Frenning G. Efficient Voronoi volume estimation for DEM simulations of granular materials under confined conditions. *MethodsX*, 2:79–90, 2015.
4. Hellrup, J, Alderborn, G and Mahlin, D. Inhibition of Recrystallization of Amorphous Lactose in Nanocomposites Formed by Spray-Drying. *Journal of Pharmaceutical Sciences*, 2015, 104, 3760-3769
5. Jonsson, H., Gråsjö, J, Nordström, J, Johansson, N, Frenning G. An apparatus for confined triaxial testing of single particles. *Powder Technol.*, 270:121–127, 2015.
6. Rubensson, J-E, Söderström, J, Binggeli, C, Gråsjö, J, Andersson, J, Sâthe, C, Hennies, F, Bisogni, V, Huang, Y, Olalde, P, Schmitt, T, Strocov, V N, Föhlisch, A, Kennedy, B, and Pietzsch, A, Rydberg-Resolved Resonant Inelastic Soft X-Ray Scattering: Dynamics at Core Ionization Thresholds, *Phys. Rev. Lett.*, 2015, 114, 133001
7. Pietzsch, A, Nisar, J, Jämstorp, E, Gråsjö, J, Århammar, C, Ahuja, R and Rubensson, J-E. Kaolinite: Defect defined material properties – A soft X-ray and first principles study of the band gap, *Journal of Electron Spectroscopy and Related Phenomena*, 2015 202, 11–15
8. Persson, A.-S., and Frenning G. An experimental evaluation of discrete element simulations of confined powder compression using an extended truncated-sphere model, *Powder Technology*, 2015, 284, 257-264
9. Nordström, J. and Alderborn, G. The granule porosity controls the loss of compactibility for both dry- and wet-processed cellulose granules but at different rate. *J. Pharm. Sci.* 104, 2015, 2029-2039.

Publications, reviews and book chapters 2014

1. Alhalaweh, A, Alzghoul, A, Kaialy, W, Mahlin, D and Bergström, CAS. Computational predictions of glass-forming ability and crystallization tendency of drug molecules. *Molecular Pharmaceutics*, 2014, 11 (9), 3123.

2. Alzghoul, A, Alhalaweh, A, Mahlin, D and Bergström, C.A.S. Experimental and Computational Prediction of Glass Transition Temperature of Drugs. *Journal of Chemical Information and Modeling*, 2014, 54 (12) 3396.
3. Berglin Engmér, C, Laurell, G, Bramer, T, Edsman, K, Counter, SA, Klason, T and Ekborn, A. Magnetic Resonance Imaging of the Middle and Inner Ear After Intratympanic Injection of a Gadolinium-Containing Gel. *Otology and Neurotology*, 2014, 35 (3), 526.
4. Widenbring, R, Frenning, G and Malmsten, M. Chain and Pore-Blocking Effects on Matrix Degradation in Protein-Loaded Microgels. *Biomacromolecules*, 2014, 15 (10), 3671.
5. Heidarian Höckerfelt M and Alderborn G. The crystallinity of cellulose controls the physical distribution of sorbed water and the capacity to present water for chemical degradation of a solid drug. *International journal of pharmaceutics* 2014, 477, 326.
6. Frenning G. From powders to tablets. Pan European Networks: Science & Technology 11, 164–165 (2014).
7. Frenning G. Predicting particulate processes. Pan European Networks: Science & Technology 12, 206–207 (2014).
8. Frenning G. Modelling implications. Pan European Networks: Science & Technology 13, 202–203 (2014).

Publications, reviews and book chapters 2013

1. Frenning, G. Towards a mechanistic model for the interaction between plastically deforming particles under confined conditions: A numerical and analytical analysis. *Materials letters*, 2013, 92, 365.
2. Mahlin, D and Bergström, CAS. Early drug development predictions of glass-forming ability and physical stability of drugs. *European Journal of Pharmaceutical Sciences*, 2013, 49 (2), 323.
3. Mahmoodi, F, Klevan, I, Nordström, J, Alderborn, G and Frenning, G. A comparison between two powder compaction parameters of plasticity: The effective medium A parameter and the Heckel 1/K parameter. *International Journal of Pharmaceutics*, 2013, 453 (2), 295.
4. Månsson, R, Frenning, G and Malmsten, M. Factors Affecting Enzymatic Degradation of Microgel-Bound Peptides. *Biomacromolecules*, 2013, 14 (7), 2317.
5. Nordström, J, Persson, A-S, Lazorova, L, Frenning, G and Alderborn, G. The degree of compression of spherical granular solids controls the evolution of microstructure and bond probability during compaction. *International Journal of Pharmaceutics*, 2013, 442 (1-2), 3.
6. Onneby, K, Pizzul, L, Bjerketorp, J, Mahlin, D, Håkansson, S and Wessman, P. Effects of di- and polysaccharide formulations and storage conditions on survival of freeze-dried *Sphingobium* sp. *World Journal of Microbiology & Biotechnology*, 2013, 29 (8), 1399.

7. Pazesh, S, Heidarian Höckerfelt, M, Berggren, J, Bramer, T and Alderborn, G. Mechanism of Amorphisation of micro-particles of griseofulvin during powder flow in a mixer. *Journal of Pharmaceutical Sciences*, 2013, 102 (11), 4036.
8. Persson, A-S and Frenning, G. The influence of rolling friction on the shear behavior of non-cohesive pharmaceutical granules: An experimental and numerical investigation. *European Journal of Pharmaceutical Sciences*, 2013, 49 (2), 241.
9. Alderborn, G. Tablets and compaction. In: Aulton's *Pharmaceutics – The design and manufacture of medicines*. 4th ed. (Ed: Aulton, ME and Taylor, KMG), Churchill Livingstone, Edinburgh, 2013.

Funding

The group receives funding from the Swedish Research Council and from Industry.

Presentations at symposia and congresses 2015

1. Frenning, G. From single-particle mechanics to discrete element simulations of confined powder compaction. Compaction Simulation Forum, Copenhagen, Denmark, June 15–17, 2015.
2. Frenning G. From granules to tablets: new contact models and simulation tools for confined powder compression. Drug Processing and Delivery, Uppsala, May 6-7, 2015.
3. Hellrup J. and Mahlin D. Recrystallization Kinetics of Amorphous Lactose in Lactose/Na⁺-montmorillonite and Lactose/Cellulose Nanowhisiker Nanocomposites. AAPS Annual Meeting, Orlando, FL, USA, October 25 – 29, 2015
4. Hellrup J. and Mahlin D. Humidity Sorption in Amorphous Lactose/Na⁺-montmorillonite Nanocomposites. AAPS Annual Meeting, Orlando, FL, USA, October 25 – 29, 2015
5. Hellrup J. and Mahlin D. Inhibition of recrystallization of amorphous lactose. Drug Processing and Delivery, Uppsala, May 6-7, 2015.
6. Hellrup J. and Mahlin D. Inhibition of recrystallization of amorphous lactose. The Fourth Annual Nordforsk Researcher Meeting, Copenhagen, January 21-23, 2015.
7. Pazesh S., Lazorova L., Berggren J., Alderborn G., and Gråsjö J. Determination of amorphous content in milled lactose using Raman spectroscopy. Drug Processing and Delivery, Uppsala, May 6-7, 2015.
8. Alderborn, G. Analytical powder compression. The 4th Compaction simulation forum. Copenhagen, June 15-17, 2015.
9. Alderborn, G. Analytical powder compression and applications in formulation development. Drug Processing and Delivery, Uppsala, May 6-7, 2015. Persson A-S., Nordström J., Frenning G. and Alderborn, G. Compression analysis for assessment of pellet plasticity. 7th International Granulation Workshop, Sheffield, U.K. July 1-3, 2015.

10. Persson A-S. and Alderborn G. Prediction of powder compactibility using analytical powder compression-initial concept evaluation. Drug Processing and Delivery, Uppsala, May 6-7, 2015.
11. Ahmed H., Alderborn G., Velaga S. and Persson A-S. Mechanical characterization of solid forms of paracetamol by analytical powder compression. The Fourth Annual Nordforsk Researcher Meeting, Copenhagen, January 21-23, 2015.

Pharmacoepidemiology and Pharmacoeconomics

Professor Dag Isacson

For most drugs the effectiveness in clinical practice is lower than predicted from the results in clinical trials. Figure 1 shows the development of drugs from the initial idea to use in clinical practice. There are several reasons for the discrepancy. In controlled trials the drug is tested on homogeneous and well-diagnosed patient groups. Dosages, adherence and adverse drug reactions (ADRs) are monitored carefully and the effect of the treatment is continuously evaluated. When the drug is registered, marketed and subsequently used in clinical practice, circumstances are vastly different. Drug treatment is given to heterogeneous patient groups, in some cases with co-morbid diseases. There may be problems with treatment adherence, interactions and prescribed dosages. The effect of drugs used in real life clinical practice is named effectiveness in order to separate it from the efficacy recorded in clinical trials.

Factors that influence the use of drugs in clinical practice can be divided into environmental/societal factors and individual factors. Environmental/societal factors include the health care system, the drug distribution system, doctors, pharmacists and other health care professionals as well as family, friends, media and marketing. Individual factors are morbidity, adherence, attitudes, knowledge, expectations as well as gender, age, education, socioeconomic factors, life style, employment and household situation. Knowledge in this field is still scarce and research has increased considerably during the last decades.

The aim of the research in the group is to contribute to drug treatment with a higher quality and effectiveness– from clinical and economical perspectives – for both the patient and for society at large. Key issues are need, demand, use and outcome of drug treatment and pharmaceutical services.

The development of research methods is crucial. New statistical methods for analyzing longitudinal data, as well as various techniques for multivariate analyses are adapted for use in the study of outcomes of drug treatment. Another area is health economics where we focus on population based studies on use of drugs, health and quality of life. In our research we have also employed results from qualitative research to develop survey questions used in quantitative research.

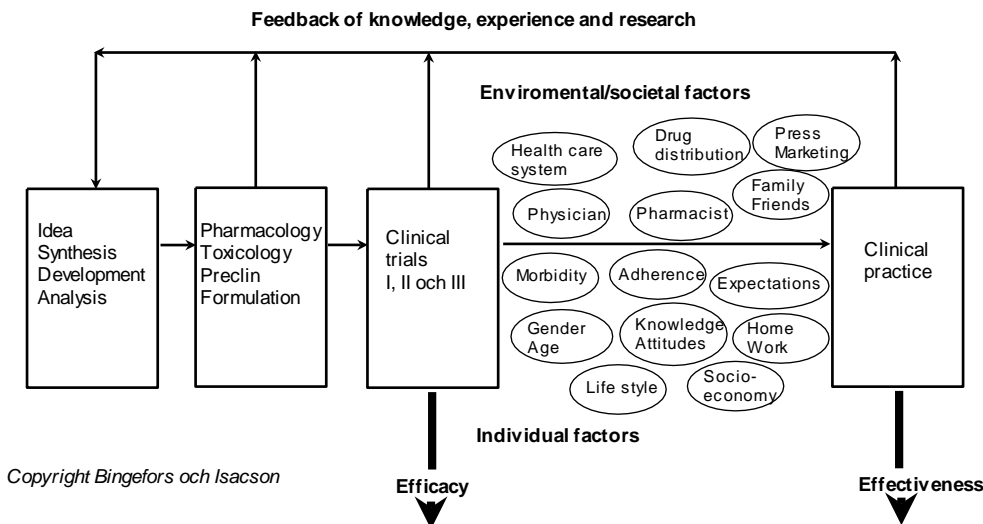


Figure 1. The development of drugs and efficacy/effectiveness of drug treatment

Swedish Health 2012

In 1994/95 a large cross-sectional study on health, quality of life and use of drugs was carried out by the research group on a random sample of the population in the county of Uppland, Sweden. In 2004/05 a similar large cross-sectional survey was conducted this time on a random sample of Sweden as a whole. Many research articles and other information have been published based on these surveys. During the last couple of years much effort from the research group has been put into the planning, financing, as well as conducting a new cross-sectional survey named "Swedish Health 2012". The survey which was administered by Statistics Sweden (SCB) was carried out during the autumn and winter 2012/13 on a random sample of 16000 individuals aged 18-84 years in Sweden. The respondents had the possibility to answer the questionnaire by using the net or the postal mail service. Information from the national prescription register as well as information from other national registers has been linked to the project. The data collection was anonymous and the project complies with the national research ethics legislation (Regional Ethical Review Board – Uppsala, Dnr 2012/073). The project enables further studies on health, quality of life and various aspects on the use of drugs in the Swedish general population.

Project areas 1: Psychiatric diseases, pain, use of drugs and quality of life

One area of interest is psychiatric diseases, pain, use of drugs and quality of life in the population. During the years several studies have focused on various types of pain, use of analgesics and quality of life, e.g. from a gender perspective. Depression and its impact on population health is another key area for the group. The close association between pain and depressive symptoms is studied on a population level.

Further, analyses are carried out on differences between men in women with respect to responsibilities for household work, employment, education, income and size of

community and how these factors are associated with health, use of medication and perceived quality of life.

Project area 2: Dermatology and treatment of skin diseases in the population

Over the years research has also been conducted in dermatology. In ongoing studies the focus is on the occurrence of dermatological problems in the population, treatment patterns and their impact on quality of life. (In collaboration with Professor Magnus Lindberg, Örebro University)

Project area 3: Adverse drug reactions and drug related problems in the general population.

Studies on adverse drug reactions in the general population have been carried out. Based on our Swedish cross-sectional survey on health, quality of life and the use of drugs in 2004/2005 a study of subjectively experienced adverse drug reactions and their association with self-perceived health status was concluded. With access now to data from our cross-sectional survey “Swedish Health 2012” (see above) further studies on adverse drug reactions as well as drug related problems are under way. Health related quality of life among users of antihypertensive drugs is also being studied.

Project area 4: Treatment adherence from a gender perspective with particular emphasis on depression and anxiety. (PhD-project Lena Thunander Sundbom).

Two studies with focus on adherence to prescribed medication regimens have been carried out based on the cross-sectional survey performed in the Swedish population 2004/05. One study analysed gender differences in non-adherent behaviour patterns and reasons for non-adherence (NA) and the other study analysed the associations between symptoms of anxiety and/or depression and non-adherent behavior patterns and reasons for NA.

Members of the group during 2015

Dag Isacson, Professor

Kerstin Bingefors, Associate professor

Helena Wennborg, MD PhD

Lena Thunander Sundbom, Licentiate, PhD student

Publications, reviews and book chapters 2014

1. Lindberg, M, Isacson, D and Bingefors, K. Self-reported Skin Diseases, Quality of Life and Medication Use : A Nationwide Pharmaco-epidemiological Survey in Sweden. *Acta Dermato-Venereologica*, 2014, 94 (2), 188.

Publications, reviews and book chapters 2013

1. Bingefors, K, Svensson, Å, Isacson, D and Lindberg, M. Self-reported lifetime prevalence of atopic dermatitis and co-morbidity with asthma and eczema in adulthood: a population-based cross-sectional survey. *Acta Dermato-Venereologica*, 2013, 93 (4), 438.
2. Edvinsson, D, Lindström, E, Bingefors, K, Lewander, T and Ekselius, L. Gender differences of axis I and II comorbidity in subjects diagnosed with attention-deficit hyperactivity disorder as adults. *Acta Neuropsychiatrica*, 2013, 25 (3), 165.
3. Lindberg, M, Bingefors, K, Meding, B and Berg, M. Hand eczema and health-related quality of life; a comparison of EQ-5D and the Dermatology Life Quality Index (DLQI) in relation to the hand eczema extent score (HEES). *Contact Dermatitis*, 2013, 69 (3), 138.
4. Thunander Sundbom, L and Bingefors, K. The influence of symptoms of anxiety and depression on medication nonadherence and its causes: a population based survey of prescription drug users in Sweden. *Patient Preference and Adherence*, 2013, 7, 805.

Other information

Dissertations

1. Ronja Månsson, Microgel interactions with peptides and proteins – Consequences of peptide and microgel properties. PhD thesis from the Faculty of Pharmacy 196, 2015.
2. Heidarian Höckerfelt, M. On the chemical and processing stability of pharmaceutical solids – Solid form dependent water presenting capacity and process induced solid form transformation. PhD thesis from the Faculty of Pharmacy 203, 2015.

Awards 2015

Holmboe M., Fagerberg J.H., Anwar J., Bergström C.A.S. Lipoidal structures present in simulated intestinal fluids modeled by molecular dynamics simulations. PhysChem Forum, Jan 28 - 29, 2015, Uppsala, Sweden. (Best poster award)

Vildhede, A. Graduate Student Research Award in Pharmacokinetics, Pharmacodynamics and Drug Metabolism and Clinical Pharmacology and Translational Research by, the American Association of Pharmaceutical Scientists, October 25-29, 2015, Florida, USA.

Fellowships

Alderborn, G: Member of the Royal Society of Sciences at Uppsala

Artursson, P: Fellow of the American Association of Pharmaceutical Scientists

Lennernäs, H: Fellow of the American Association of Pharmaceutical Scientists

Malmsten, M: Fellow of the Royal Society of Chemistry. Member of the Royal Swedish Academy of Engineering Sciences (IVA)

Addresses 2016

Department of Pharmacy

Uppsala University, BMC, Box 580, SE-751 23 Uppsala, Sweden

Tel +46 18 471 4472

Fax +46 18 471 4223

www.farmfak.uu.se/farm

Ahnfelt Emelie	emelie.ahnfelt@farmaci.uu.se
Alderborn Göran	goran.alderborn@farmaci.uu.se
Alhalaweh Amjad	amjad.alhalaweh@farmaci.uu.se
Alskär Linda	linda.alskar@farmaci.uu.se
Alvarmo Charlotta	charlotta.alvarmo@farmaci.uu.se
Alvebratt Caroline	caroline.alvebratt@farmaci.uu.se
Andersson Sara	sara.andersson@farmaci.uu.se
Artursson Per	per.artursson@farmaci.uu.se
Backlund Maria	maria.backlund@farmaci.uu.se
Baranczewski Pawel	pawel.baranczewski@farmaci.uu.se
Bergström Christel	christel.bergstrom@farmaci.uu.se
Magnus Bergström	magnus.bergstrom@farmaci.uu.se
Bingefors Kerstin	chris.bingefors@farmaci.uu.se
Björk Erik	erik.bjork@farmaci.uu.se
Browning Kathryn	kathryn.browning@farmaci.uu.se
Cai Yanling	yanling.cai@farmaci.uu.se
Colombo Stefano	stefano.colombo@farmaci.uu.se
Dahlgren David	david.dahlgren@farmaci.uu.se
Dubbelboer Ilse	ilse.dubbelboer@farmaci.uu.se
Eriksson Johanna	johanna.eriksson@farmaci.uu.se
Fagerberg Jonas	jonas.fagerberg@farmaci.uu.se
Frenning Göran	goran.frenning@farmaci.uu.se
Gaugaz Fabienne	fabienne.gaugaz@farmaci.uu.se
Gernandt Jonas	jonas.gernandt@farmaci.uu.se
Gråsjö Johan	johan.grasjo@farmaci.uu.se

Handin Niklas	niklas.handin@farmaci.uu.se
Hansson Per	per.hansson@farmaci.uu.se
Hellrup Joel	joel.hellrup@farmaci.uu.se
Holmboe Michael	michael.holmboe@farmaci.uu.se
Isacson Dag	dag.isacson@farmaci.uu.se
Jidheden Claes	claes.jidheden@farmaci.uu.se
Johansson Karin	karin.johansson@farmaci.uu.se
Jonsson Henrik	henrik.jonsson@farmaci.uu.se
Karlgren Maria	maria.karlgren@farmaci.uu.se
Khan Elin	elin.khan@farmaci.uu.se
Khodus Georgiy	Georgiy.khodus@farmaci.uu.se
Larsson Per	per.larsson@farmaci.uu.se
Larsson Pernilla	pernilla.larsson@farmaci.uu.se
Lazorova Lucia	lucia.lazorova@farmaci.uu.se
Lennernäs Hans	hans.lennernas@farmaci.uu.se
Lilienberg Elsa	elsa.lilienberg@farmaci.uu.se
Lundkvist Jonas	jonas.lundkvist@farmaci.uu.se
Lundquist Patrik	patrik.lundquist@farmaci.uu.se
Lyngå Heléne	helene.lynga@farmaci.uu.se
Magnusson Christin	christin.magnusson@farmaci.uu.se
Mahlin Denny	denny.mahlin@farmaci.uu.se
Malmsten Martin	martin.malmsten@farmaci.uu.se
Mastej Maria	maria.mastej@farmaci.uu.se
Mateus André	andre.mateus@farmaci.uu.se
Matsson Pär	par.matsson@farmaci.uu.se
Nises Ahlgren Eva	eva.nises-ahlgren@farmaci.uu.se
Nordström Josefina	josefina.nordstrom@farmaci.uu.se
Nordström Randi	randi.nordstrom@farmaci.uu.se
Nyström Lina	lina.nystrom@farmaci.uu.se
Ocklind Göran	goran.ocklind@farmaci.uu.se
Pazesh Samaneh	samaneh.pazesh@farmaci.uu.se
Persson Ann-Sofie	ann-sofie.persson@farmaci.uu.se
Roos Carl	carl.roos@farmaci.uu.se

Rudén Jonas	jonas.ruden@farmaci.uu.se
Saleh Aljona	aljona.saleh@farmaci.uu.se
Simoff Ivailo	ivailo.simoff@farmaci.uu.se
Singh Shalini	shalini.singh@farmaci.uu.se
Sjögren Erik	erik.sjogren@farmaci.uu.se
Stenlund Jannike	jannike.stenlund@farmaci.uu.se
Svensson Richard	richard.svensson@farmaci.uu.se
Svensson Lindgren Annette	annette.svensson-lindgren@farmaci.uu.se
Thormann, Ursula	ursula.thormann@farmaci.uu.se
Thunander Sundbom Lena	lena.thunander-sundbom@farmaci.uu.se
Treyer Andrea	andrea.treyer@farmaci.uu.se
Wahlberg Lise-Britt	lise-britt.wahlberg@farmaci.uu.se
Wegler Christine	christine.wegler@farmaci.uu.se
Wennborg Helena	helena.wennborg@farmaci.uu.se
Widenbring, Ronja	ronja.widenbring@farmaci.uu.se
Wisell Kristin	kristin.wisell@farmaci.uu.se
Wästberg Galik Ulla	ulla.wastberg-galik@farmaci.uu.se
Öjefors-Stark Katarina	katarina.ojefors-stark@farmaci.uu.se
Ölander Magnus	magnus.olander@farmaci.uu.se