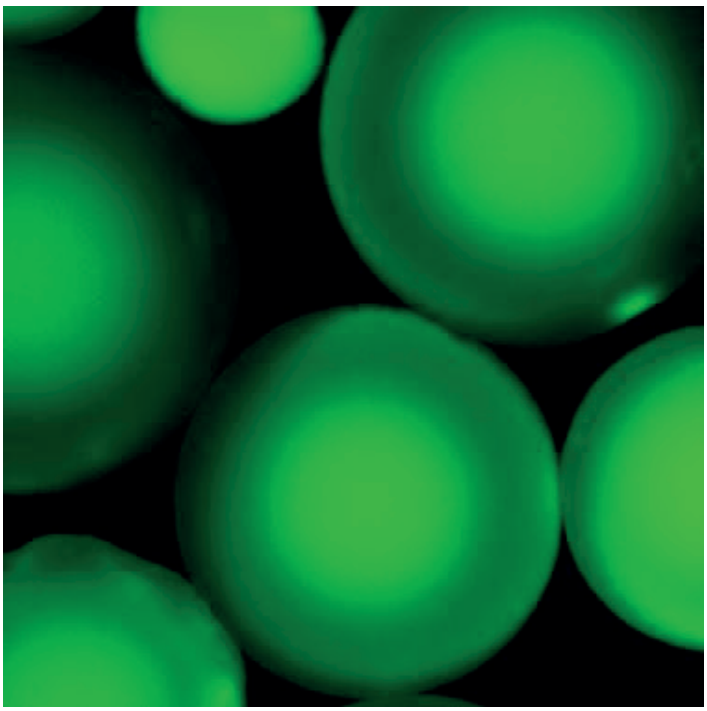
UPPSALA UNIVERSITET

Department of Pharmacy

ANNUAL REPORT 2014



Department of Pharmacy

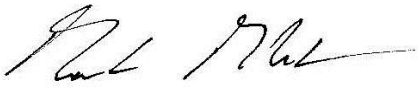
ANNUAL REPORT 2014

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 2015-03-16



Martin Malmsten

Chairman, Department of Pharmacy

List of Contents

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 2014, considerable activities have been devoted to developing new programmes for the Bachelor and Master programmes. The work has involved the entire Faculty of Pharmacy, as well as input from our Advisory Group and other stakeholders. While we are still only underway in 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 2014, personnel situation at the department has been stable from a personnel turnover perspective. With our spread of teaching activites, 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 2014 allowed for continued strategic investments in research infrastructure. 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 2014 (kSEK)

University funding - Undergraduate teaching	17 062
Contract teaching	797
University funding - Research and post-graduate teaching	25 742
Research grants	13 814
Commissioned research	2 321
Total	59 736

Organization and personnel

Organization

Chairman

Martin Malmsten

Deputy chairman

Per Artursson/Erik Björk

Department board

Martin Malmsten, chairman
Göran Alderborn, teacher representative
Per Hansson, teacher representative
Erik Björk, teacher representative, deputy
Christin Magnusson, teacher representative
Christel Bergström, teacher representative
Göran Frenning, teacher representative, deputy
Johan Gråsjö, representative for technical/administrative personnel, deputy
Richard Svensson, representative for technical/administrative personnel
Elsa Lilienberg, graduate student representative
Ronja Widenbring, graduate student representative (Jan-June)
Linda Alskär, graduate student representative (July-Dec)
Anna Vildhede, graduate student representative, deputy (Jan-June)
Lina Nyström, graduate student representative, deputy (July-Dec)
Lukas Löfling, student representative (Jan-June)
Kia Ropponen, student representative (July-Dec)
Eva Nises Ahlgren, secretary

Director of administration

Eva Nises Ahlgren

Director of graduate studies

Per Artursson/Göran Frenning

Directors of undergraduate studies

Kerstin Bingefors
Anders Ericsson/Jonas Gernandt
Ida Bergström
Christin Magnusson

Computers and web

Göran Ocklind

Personnel

Senior staff

Bertil Abrahamsson, PhD, Adjunct professor
Göran Alderborn, PhD, Professor in Pharmaceutical Technology
Per Artursson, PhD, Professor in Dosage Form Design
Christel Bergström, PhD, Associate professor
Ida Bergström, MSc, Lecturer
Kerstin Bingefors, PhD, Senior lecturer
Erik Björk, PhD, Senior lecturer
Ragnar Ek, PhD, Associate professor
Anders Ericsson, PhD, Associate professor
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, Assistant professor
Martin Malmsten, PhD, Professor in Pharmaceutical Physical Chemistry
Pär Matsson, PhD, Assistant professor
Mats Nordal, MSc, Guest lecturer
Erik Sjögren, PhD, Senior lecturer
Jannike Stenlund, MSc, Lecturer
Lena Strindelius, PhD, Senior lecturer
Helena Wennborg, MD PhD, Guest lecturer
Katarina Öjefors-Stark, PhD, Lecturer

PhD Students	Supervisors
Emelie Ahnfelt	Hans Lennernäs
Linda Alskär	Christel Bergström
Sara Andersson	Christel Bergström

David Dahlgren	Hans Lennernäs
Ilse Dubbelboer	Hans Lennernäs
Jonas Fagerberg	Christel Bergström
Mina Heidarian Höckerfelt	Göran Alderborn
Joel Hellrup	Denny Mahlin
Claes Jidheden	Per Hansson
Henrik Jonsson	Göran Frenning
Elsa Lilienberg	Hans Lennernäs
André Mateus	Per Artursson
Randi Nordström	Martin Malmsten
Lina Nyström	Martin Malmsten
Samaneh Pazesh	Göran Alderborn
Carl Roos	Hans Lennernäs
Shalini Singh	Martin Malmsten
Andrea Treyer	Per Artursson
Christine Wegler	Per Artursson
Anna Vildhede	Per Artursson
Ronja Widenbring	Martin Malmsten
Kristin Wisell	Sofia Kälvemark Sporrong
Magnus Ölander	Per Artursson

PhD Student, external	**Supervisor**
Pia Frisk	Sofia Kälvemark Sporrong
Lena Thunander Sundbom	Kerstin Bingefors

Research scientists

Amjad Alhalaweh, PhD
Maria Backlund, PhD
Pawel Baranczewski, PhD
Stefano Colombo, PhD
Fabienne Gaugaz, PhD
Michael Holmboe, PhD
Maria Karlgren, PhD

Lucia Lazorova, PhD
Patrik Lundquist, PhD
Josefina Nordström, PhD
Christian Pedersen, PhD
Ann-Sofie Persson, PhD
Aljona Saleh, PhD
Ivailo Simoff, PhD
Erik Sjögren, PhD
Richard Svensson, PhD
Carrie Tsoi, PhD

Administrative and technical staff

Maria Enarsson
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

Mini-biographies of permanent staff (January 1st 2015)

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 amophisation of particles.

Examples of current commitments

- Dean of the Faculty of 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
- Node-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 approache 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, pharmaceutics and biopharmaceutics. 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. Further, Chris Bingefors is active in pharmacy practice research.

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 pharmaco-economics

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

- Chairman of the Committee of Education at the Faculty of Pharmacy, Uppsala University

- Vice Dean at the Faculty of Pharmacy, Uppsala University
- Member of the board of Section for Pharmaceutics and Biopharmaceutics. The Swedish Academy of Pharmaceutical Sciences, Stockholm

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 catanionic 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
- Deputy member of the of the Board of 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 surfactant self-assemblies in aqueous systems. Current focus is on the interaction between proteins/peptides and oppositely charged microgel networks and its implications on microgels as carriers of protein drugs and mechanisms of protein sorting. Of special interest is 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
- Member of the Board of the Department of Pharmacy
- Member of the group for the development of new pharmacist programs at 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.

Examples of current commitments

- Member of the editorial panel for The Annals of Pharmacotherapy

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 diseaseas.

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 use of the amorphous form of formulation components and the possibility to develop amorphous nano-composites are studied.

Examples of current commitments

- Scientific Advisor to the Editors of JPharmSci
- Member of the Board of Farmacins Alumnförening, Department of Pharmacy, Uppsala University
- 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 and lipid and polymer systems through novel developments in both conceptual understanding and analytical opportunities in self-assembly and responsiveness of such 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 Board of XImmune AB
- 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 and physiological based drug delivery and targeting. The long-term goal is to improve pharmacological effect and therapeutic outcome by reaching the active site and/or specific organ with high drug concentration at the right time and thereby avoiding 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 of carrier-mediated membrane transport and intracellular enzymatic processes. The disease-oriented projects have their targets in the hepatobiliary system, endocrinology, various tumour tissues and other target organs. Local modified release drug therapy is a particular strong focus in the oncology research project. Another strong research effort is to understand in the in vivo mechanisms determining gastrointestinal drug absorption, liver first-pass effect and biliary excretion. These finding are the 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 treatements for liver cancer taking the role of local disposition in a diseased tissue into account. Buidling physiological based pharmacokinetic modelling with appluication to predicting and understanding the local dispistion 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 examining 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 a 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 effecicient and safe local chemotherapy is developed.

Professor Lennernäs is the inventor of more than 15 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. The product, Rapinyl®, has been approved in EU and USA. He has also together with co-inventors initiated three start-up companies that has developed a novel oral replacement therapy (www.duocort.com) for Addison disease, the development of local drug treatment of localised prostate cancer (www.liddspharma.com) and novel treatements for metabolic/endocrinological diseases.

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 and collaborators Uppsala University hospital, University of Mainz, University of Michigan and National Vetrinary Institute. Internal collaborators are Prof Martin Malmsten 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, Assoc Prof Niklas Axén and collaborators at Uppsala University hospital, Karolinska University hospital, Tamperer University hospital, Helsinki Universityu hospital, and National Vetrinary Institute

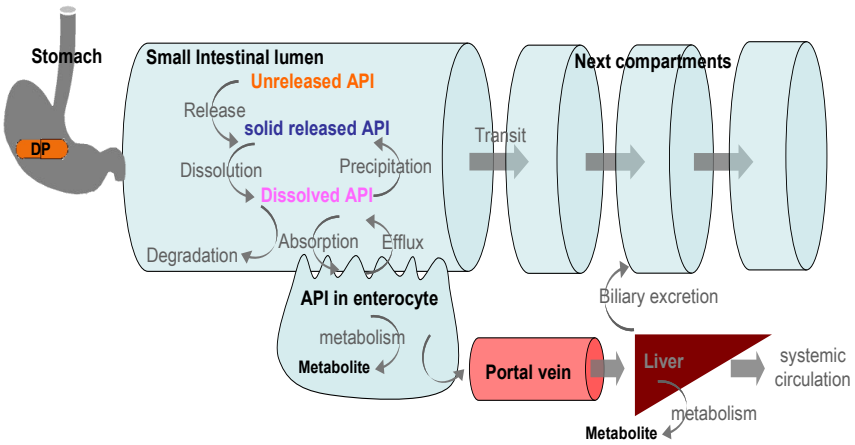


Figure 1. OrBiTo is new Eurpean project within the IMI programme in the area oral biopharmaceutics tool that include nine universities, one regulatory agency, one non-profit research organisation, three SMEs together with the twelve pharmaceutical companies (http://www.imi.europa.eu/content/orbito). 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 2014

Hans Lennernäs, Professor

Bertil Abrahamsson, Professor in industrial biopharmaceutics

Erik Sjögren, Research scientist

Emelie Ahnfelt, PhD Student

David Dahlgren, PhD Student

Ilse Dubbelboer, PhD Student

Elsa Lilienberg, PhD Student

Carl Roos, PhD Student

Publications, reviews and book chapters 2014

1. 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.

2. Berthelsen, R, Sjögren, E, Jacobsen, J, Kristensen, J, Holm, R, Abrahamsson, B and Mullertz, 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.

3. 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.

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Presentations at symposia and congresses 2014

1. Lennernäs H. GI Fluid and Cellular Transport and Metabolism Oral In Vivo Predictive Dissolution (IPD) Methodologies, University of Michigan, Ann Arbor, August 4-6, 2014.
2. Lennernäs H. Drug delivery based drug development – does it affect the pace of pharmaceutical innovation? Läkemedelsakademin April 1, Uppsala3 Lennernäs H. Food Drug Interactions Caused by Drug Transporter and Drug Enzyme Interplay, Orbito PhD course, Mainz, September 18.
3. Sjögren E, Tammela TLJ, Lennernäs B, Malmsten L, Axén N and Lennernäs H. A theoretical model describing the tissue permeation of 2-hydroxyflutamide in the human prostate gland following local administration of an injectable depot formulation. Nature Biotechnology-Roche conference, September 3-5, Zug, Switzerland.
4. Erik Sjögren. Which Information is Required to Develop a Controlled Release Oral Dosage Form Based on Simulation and Modeling. Presentation Predictive Biopharmaceutic Methods in Drug Discovery and Oral Drug Product Development, Mainz, Germany, 17-19 September.
5. Erik Sjögren. In silico predictions of intestinal drug absorption and oral bioavailability. Predictive chemistry in drug discovery and development. AstraZeneca 25 September.
6. Erik Sjögren. Application of in silico methods for biopharmaceutical assessments. Lunch seminar - Institutionen för farmaci, Uppsala universitet. 22 October.
7. Dahlgren, D. Compilation and analysis of human in vivo intestinal permeability data. Poster Orbito meeting Stevenage 12-14 may. David Dahlgren & Carl Roos, Erik Sjögren, Christer Tannergren, Bertil Abrahamsson, Hans Lennernäs.
8. Dahlgren, D. Compilation and analysis of human in vivo intestinal permeability data. Poster Predictive Biopharmaceutic Methods in Drug Discovery and Oral Drug Product Development, Mainz, Germany, 17-19 September. David Dahlgren & Carl Roos, Erik Sjögren, Christer Tannergren, Bertil Abrahamsson, Hans Lennernäs.
9. Erik Sjögren. Quantitation of regional intestinal permeability from human drug absorption studies Poster Orbito meeting Stevenage 12-14 may. Erik Sjögren, Carl Roos, David Dahlgren and Hans Lennernäs.
10. Roos, C. Determining rat intestinal permeability by cassette-dosing in the Ussing chamber. Poster Orbito meeting, Stevenage, UK, 12-14 May. Carl Roos, David Dahlgren, Erik Sjögren, Christer Tannergren, Bertil Abrahamsson, Hans Lennernäs.
11. Roos, C. Determining rat intestinal permeability by cassette-dosing in the Ussing chamber. Poster Predictive Biopharmaceutic Methods in Drug Discovery and Oral Drug Product Developen, Mainz, Germany, 17-19 September. Carl Roos, David Dahlgren, Erik Sjögren, Christer Tannergren, Bertil Abrahamsson, Hans Lennernäs.
12. Ahnfelt, E., Axén, N., Sjögren, E., Lennernäs, H. In vitro release and theoretical modeling of a selection of formulations in modified mini-IDR discs, oral presentation, NordForsk, Uppsala, Sweden, January 29-31.

13. Ahnfelt, E., Axén, N., Sjögren, E., Lennernäs, H. Development of a novel in vitro drug release test method for parenteral formulations, Poster, PhysChem Forum, London, UK, April 9-10.
14. Ahnfelt, E., Axén, N., Sjögren, E., Lennernäs, H. In vitro release and theoretical modeling of a selection of formulations in modified mini-IDR™ holders Poster, Controlled Release Society annual conference, Chicago, US, July 13-16.
15. Dubbelboer, I.R., Lilienberg, E., Sjögren, E., Lennernäs, H. A Semi-PBPK Model Explaining the in vivo Hepatobiliary Behavior of Doxorubicin from Drug Delivery Systems Used for TACE-Treatment. Electronic Poster, International Liver Cancer Association 8th annual conference. Kyoto, Japan. September 5-7.
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17. Lilienberg, E. The Effect of Lipiodol and Cyclosporine on the Hepatobiliary Disposition of Doxorubicin. Oral Presentation, Nordforsk, January 31, 2014, Uppsala, Sweden.
18. Abrahamsson, B. Invited speaker. 5th FIP Pharmaceutical *Sciences* World Congress, Melbourne April 2014.
19. Abrahamsson, B. Invited speaker. EUFEPS conference on Development of a guideline on therapeutic equivalence for locally applied and locally acting products in the GI, Berlin June 2014.
20. Abrahamsson, B. Invited speaker. In Vivo Predictive Dissolution Conference, Ann Arbour University of Michigan, Aug 2014.
21. Abrahamsson, B. Invited speaker.OrBiTo workshop, University of Mainz, Sept 2014.

Patents and patents applications

More than 15 patents and patents applications..

Drug Delivery

Professor Per Artursson

Drug Delivery Group

In 2014, the drug delivery group went through exciting developments. These included co-publications in top ranked journals and new prestigious grants, such as the young ERC award to associate professor Christel Bergström and an assistant professorship from the medical and pharmaceutical faculties to Dr Pär Matsson. The participation of our UDOPP platform in the Drug Discovery and Development platform within SciLifeLab, as well as participation in the Innovative Medicines Initiative ENABLE allowed recruitment of new staff and purchase of urgently needed equipment. Finally, six group members received scientific awards.

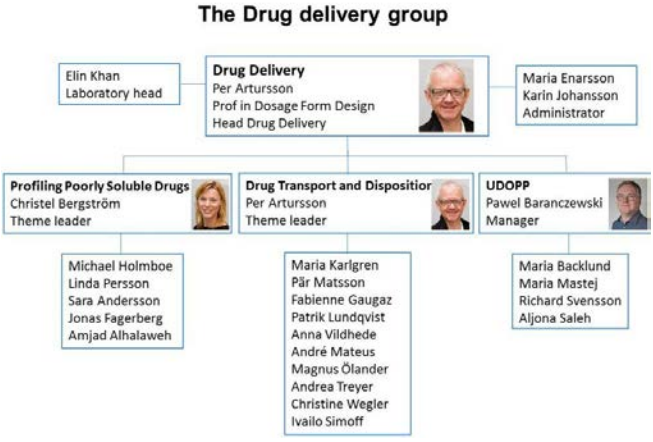

Figure 1. The drug delivery group 2014

The research in the drug delivery group is divided into three collaborating domains, fig 1. In the first domain, 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, headed by Dr Bergström, the focus is on predictive biopharmaceutics, with a focus on drug formulation, solubility and dissolution. In the third domain, 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. In summary, our research takes a multidisciplinary approach that combines computational chemistry and bioinformatics with cell- and molecular biology, biopharmaceutics, pharmaceutics 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

During 2014, the drug delivery and disposition group continued to investigate transport mechanisms in the human liver. These integral membrane proteins determine the uptake, intracellular accumulation, metabolism, target exposure and elimination of drugs. The purchase of an elutriation centrifuge allowed a better separation of the various cell types of the human liver. Global as well as targeted proteomics played an important role in the various studies. Our global proteomics studies, which are performed in collaboration with the Max-Planck Institute of Biochemistry in Martinsried, Germany, provided new insights into the human liver proteome and how it is affected in various stressful situations such as long term effects after exposure to cytostatics and effects of the isolation of liver cells on the protein expression in various subcellular organelles. Our group also contributed to the development of a new sensitive methodology for determination of peptide and protein concentration, based on tryptophan. We continued the development of the “maximal transport activity” concept and provided proof-of-concept studies of how this concept can be used to predict and quantify drug transport mechanisms and intrinsic drug clearance in individual human livers, fig 2. In addition, the methodology was used to predict drug-drug interactions of clinical relevance and to point at isotype-specific variability in the drug-drug interactions at the individual level. Finally, a mechanistic model was developed that in combination with kinetic data from our expression systems, could predict the individual contribution of uptake and efflux transporters to the overall bile secretion of a drug. The lipid lowering drug pitavastatin was used as model drug in these studies. It was found that pitavastatin is taken up by several SLC transporters from the blood and that it is effluxed by several ABC transporters both into the bile and back into the blood and that the contribution of all these transporters to the net flux of drugs from blood into bile could be perfectly modelled.

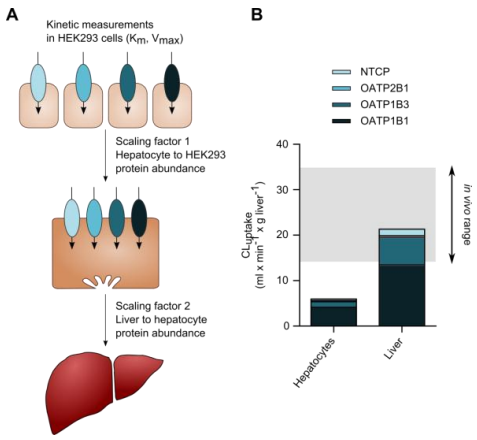

Figure 2. Quantification of protein abundance and kinetic studies in expression systems (top), provide a platform for delineating transporter contribution in human hepatocyte experiments (middle) and prediction of drug clearance in man. In fig 2B, the contribution of four uptake transporters to the uptake clearance of pitavastain in human hepatocytes is shown and is scaled to the human liver. The results are in excellent agreement with the range of reported uptake clearance values in man (shaded area in fig 2B).

The impact of drug transporting proteins on the intracellular drug exposure is another focus of interest and these studies, albeit demanding, progressed well during 2014. By combining measurements of intracellular free drug concentrations (which vary substantially between different drugs) with the recently introduced CETSA (cellular thermal shift assay) methodology that measures target engagement in intact cells, we hope to reveal how intracellular free drug concentrations are correlated with target engagement. In another study our cell based methodology for determination of intracellular drug concentrations was adopted to a high throughput format for prediction of the same in the brain.

The group also revisited the field of intestinal drug delivery. Collaborations with Norrköping hospital and Linköping University as well as with Department of Medical Sciences and Surgery in Uppsala provided freshly isolated jejunal samples for our studies. Snap-frozen samples were used for global proteomics analysis and tissues were mounted in Ussing chambers with retained barrier function as assessed with electrophysiological parameters as well as transport of probe substrates and integrity markers. The set up will be used both for studies nanoparticulate delivery systems and transport mechanisms for conventional drugs. During the year, the discussion of the role of passive and active transport across cellular membranes continued, and we challenged the recent hypothesis that all transport across membranes is carrier-mediated using a systems biology approach. Here the global transporter proteome in human intestinal epithelial Caco-2 cells was combined with kinetic parameters from our data base for a large variety of transporters. Different scenarios with carrier-mediated transport via 1 to 20 transporters were modelled, and the adherence to experimental observations typical of passive transmembrane diffusion was investigated. Only in rare cases could combinations of transporters mimic typical experimental observations, such as linear concentration dependence. Thus, it remains to be proven that all membrane transport occurs via carrier-mediated transport.

Profiling Poorly Soluble Drugs

The research performed within Dr Bergström´s group is focused on poorly soluble compounds. These challenging but interesting compounds are analyzed for their physiological solubility in the gastrointestinal tract. Further, their formulate-ability in different enabling formulations is studied with the long term goal to allow computational prediction of successful formulation pathways to efficiently reach and activate contemporary targets. The research is performed in silico and in vitro where the following three themes can be distinguished: i) Molecular features of importance for solubilization in the gastrointestinal tract. ii) Molecular structures possible to efficiently load into lipid based formulations. iii) Molecular properties of importance to allow solid state transformations of high melting drug substances with the aim to increase dissolution rate and trigger supersaturation. During 2014 the first thesis from the group was finalized. The thesis focused on dissolution profiling in biorelevant media and resulted in improved molecular understanding of compounds being efficiently solubilized by colloidal structures naturally present in the small intestinal fluids. It was found that aromatic structures suffered more from poor solubility than the aliphatic structures do, but also molecular size is a limiting factor for efficient solubilization. More importantly the first model to predict solubility in human intestinal fluids was developed, a model already implemented by the pharmaceutical industry. Enabling formulations have been studied as a means to increase the amount of drug being dissolved in the intestinal fluid and hence, increasing the driving force for absorption. During 2014 we continued to build our in-house lipid excipient solubility database which now includes more than 1000 solubility values measured in 9 excipients commonly used in lipid based drug delivery systems. The database is currently being used for computational modeling with the goal to arrive at models predicting loading capacity in complex lipid based formulations. Our work on predictive factors for glass-forming ability as indicators of which molecules that easily can be transformed to their amorphous state was during the year extended to include ~150 drug compounds. Based on this dataset it was shown that not only the glass-forming ability was possible to predict from the molecular structure of the drug but also the stability of the produced amorphous material. Further the first model for prediction of the glass transition temperature was developed.

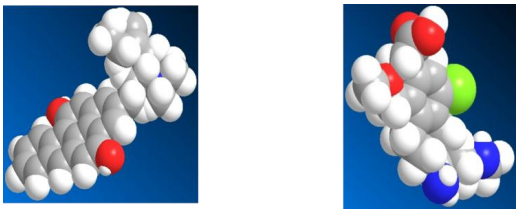

Figure 3. Molecular properties of importance for solubility in intestinal fluids. The picture to the left shows limiting factors (aromaticity, size and branching) whereas the figure to the right shows hydrogen bond donors and acceptors that are driving forces for solubilization. The hydrogen bonding/acceptor atoms were found to have the largest influence when being dispersed over the molecule, as they then form anchor points for hydration on the surface area exposed to water.

UDOPP

UDOPP is an integrated node of the Swedish national infrastructure for chemical biology (CBCS) and became in 2014 a facility (ADME of Therapeutics) within the Drug Discovery and Development Platform (DDDP) at the Science for Life Laboratories. Since February 2014, UDOPP is a partner of the Innovative Medicine Initiative (IMI) European Gram Negative Antibacterial Engine (ENABLE) consortium, within the program New Drugs for Bad Bugs (ND4BB).

With the support of DDDP funding, reconstruction of laboratories and purchase of new state of the art equipment was possible. A Hamilton Robotics STAR liquid-handling system was purchased and automation of basic ADME assays was implemented. For quantification of in vitro an in vivo samples, identification of drug metabolites as well as to enable peptide and proteomic analysis, a Sciex QTRAP 6500 mass spectrometer was purchased. Since the start of DDDP, UDOPP has supported eight projects and pre-projects with absorption, distribution, metabolism and excretion (ADME) investigations and physicochemical profiling, in order to facilitate the selection of the best drug candidate for proof-of-concept studies. Similarly, five projects in the IMI/ENABLE consortium, aiming at finding new hit and lead compounds active against gram negative bacteria, have received active support from UDOPP. Finally, within the CBCS collaborations about 15 small and large projects have received contribution of UDOPP expertise.

During 2014 UDOPP facility has significantly contributed to two highly successful projects within CBCS, which resulted in publications in Nature and Cell. Within the MTH1 project over 300 compounds were tested for their ADME properties and approximately 2500 in vivo samples were analyzed. MTH1 is a new anticancer target in vivo and the small molecules TH287 and TH588 are first-in-class nudix hydrolase family inhibitors that potently and selectively engage and inhibit the MTH1 protein in cells as well as in patient-derived mouse xenografts. The fruitful progress of this project has led to the creation of “The Helleday foundation”, a non-for-profit organization with the aim to increase research and development of new drugs. In the second example, Glioblastoma multiforme (GBM), which is a most aggressive form of brain cancer, was the target in a phenotypic screening campaign. This compound screening led to the discovery of chemical entities termed Vacquinols. Further development and characterization showed that Vacquinols attenuates disease progression and prolongs survival in a GBM animal model. UDOPP contributed to ADME and in vivo pharmacokinetics characterization on these compounds and Vacquinol-1 was found to have excellent brain exposure, a prerequisite for treatment of brain cancers. Out of this discovery a new company (Glionova) was founded, with the goal to develop efficient drugs against Glioma.

Furthermore, in order to meet the needs of the projects, development and improvements of methodologies are always required and about 10 such projects are ongoing at our facility. For instance, determination of physical-chemical properties (pka and logD) has now been improved, with the use of Sirius T3 equipment. Additionally, a high-throughput cell-based method to predict the unbound drug fraction in the brain has been developed in the lab.

Members of the group during 2014

Per Artursson, Professor

Christel Bergström, Associate professor

Amjad Alhalaweh, Research scientist

Sara Andersson, PhD Student

Maria Backlund, Research scientist

Pawel Baranczewski, Research scientist

Maria Enarsson

Jonas Fagerberg, PhD Student

Fabienne Gaugaz, Post doc

Michael Holmboe, Post doc

Karin Johansson, BSc

Maria Karlgren, Research scientist

Elin Khan, MPharm

Patrik Lundquist, Research scientist

Maria Mastej, BSc

André Mateus, PhD Student

Pär Matsson, Assistant professor

Linda Alskär, PhD Student

Ivailo Simoff, Research scientist

Richard Svensson, Research scientist

Anna Vildhede, PhD Student

Magnus Ölander, PhD Student

Aljona Saleh, Research scientist

Christine Wegler, PhD student

Andrea Treyer, PhD student

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.
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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.

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Transporter Expression on Uptake Clearance and Drug-Drug Interactions. *Drug Metabolism And Disposition*, 2014, 42 (7), 1210.

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18. 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.

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Publications, reviews and book chapters 2012

1. Artursson, P, Palm, K and Luthman, K. Caco-2 monolayers in experimental and theoretical predictions of drug transport. Republished in *Advanced Drug Delivery Reviews*. 2012, 64, 280.
2. Bergstrom, CAS, Charman, SA and Nicolazzo, JA. Computational Prediction of CNS Drug Exposure Based on a Novel In Vivo Dataset. *Pharmaceutical research*, 2012, 29 (11), 3131.
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9. Matsson, P, Giacomini, KM and Brater, DC. Renal Disposition of Drugs and Translation to Dosing Strategies. Seldin and Giebisch's The Kidney – Physiology and Pathophysiology 5th Ed. Eds: Alpern, B, Moe, OW and Caplan, M. Elsevier Press, New York, 2012, 3185.
10. Matsson, P, Yee, SW, Markova, S, Morrissey, K, Jenkins, G, Xuan, J, Jorgenson, E, Kroetz, DL and Giacomini, KM. Discovery of regulatory elements in human ATP-binding cassette transporters through expression quantitative trait mapping. *Pharmacogenomics Journal*, 2012, 12 (3), 214.
11. Norinder, U and Boström, H. Introducing uncertainty in predictive modeling: Friend or foe? *Journal of Chemical Information and Modeling*, 2012, 52 (11), 2815.

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Doctoral dissertation

Fagerberg, J. Experimental and computational predictions of drug solubility in human gastrointestinal fluids. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 187, 2014.

Awards

1. Gaugaz, FZ, Advanced Postdoc Mobility Fellowship, Swiss National Science Foundation
2. Bergström, C., Karlgren, M., Matsson, P., The Nordic Prize for Alternatives to Animal Experiments, Forska Utan Djurförsök (Sweden), Alternativfondet (Denmark) and Juliana von Wendts Stiftelse (Finland)
3. Persson, L., Student Award for Outstanding Contribution., 5th FIP Pharmaceutical Sciences World Congress
4. Vallianatou, T., Lodén, H., Nilsson, A., Shariagorji, M., Pereira, M., Svenningsson, P., Karlgren, M., Andrén, P.E., Best Poster Award, 1st International Congress: From Drug Discovery to Drug Delivery.
5. Fagerberg, J. H., GABI award for Best doctoral thesis in pharmaceutics 2013-2014, Swedish Pharmaceutical Society
6. Andersson, S.B.E. Best Poster Award, PhysChem Forum 2014, East Grinstead, UK.
7. Artursson, P., Karl Johan Öbrink lecturer 2014
8. Pedersen, J., The Rosenön Award for best thesis 2013/14 in the PKPD/metabolism field, Swedish Pharmaceutical Society

Arrangement of research seminars and courses 2014

1. Workshop: Sample preparation and quantification of protein expression by mass spectrometry, Aug 18, 2014. Speakers: Jacek Wisniewski, Max-Planck Institute,

Germany. Janne Lehtiö, Karolinska Institutet, Per Andrén, Uppsala University, Jonas Bergquist, Uppsala University, Dorothea Rutishauser, Karolinska Institutet. Organizer: Per Artursson.

2. 5th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Jan 23, 2014. Organizers: Per Artursson, Pavel Baranczewski, Patrik Lundquist, André Mateus.
3. NordForsk - The Third Annual FTPT Network Meeting, 29 – 31 January. Uppsala, Sweden. Organizers: Christel Bergström, Linda Persson, Henrik Jonsson, Sara Andersson
4. Group seminar: Dr Staffan Johansson, Uppsala University. Mechanical force-induced cell signaling via integrins. Sep 1, 2014. Host: Per Artursson
5. Group seminar: Prof Edward Le Cluyse, The Hamner institutes for health sciences, North Carolina, USA. Effects of shear on liver cells. Sep 1, 2014. Host: Per Artursson
6. Phd student course: Human Cell Culture. Methods and Applications. May 12-16, 2014. Lecturer: Roland Grafström, Karolinska Institutet. Organizers: Per Artursson, Nils Welsh and Ulf Ericsson.
7. Department seminar: Prof. Thomas Helleday, Karolinska Institutet. Novel anti-cancer treatments: from PARP to MTH1 inhibitors, May 7, 2014. Host: Pawel Baranczewski
8. Department seminar: Dr Johanna Haglund, Metsafe. Principles and significance of biotransformation and MIST studies within pharmaceutical industry. Mar 26, 2014. Host: Pawel Baranczewski
9. Department seminar: Dr Susanne Bredenberg, Orexo. The use of ceramic materials for slow release of potent drugs for the treatment of pain – a VINNOVA VinnMer project. Mar 12, 2014. Host: Christel Bergström
10. Department seminar: Prof Katarina Edwards, Uppsala University. Nuclisomes and Lipodisk – Tailored nanoparticles for effective drug delivery. Feb 25, 2014. Host: Christel Bergström
11. Department seminar: Assoc Prof Serhiy Souchelnytskyi, Karolinska Institutet. Cancer treatment: how personal does it get? - Contribution of Functional Molecular Diagnostics (FMDx). Dec 17, 2014. Host: Per Artursson

Presentations at symposia and congresses 2014

Abstracts Posters

1. Lundquist, P., Svedberg, E., Artursson, A. Ussing chambers for the study of nano-carrier permeability in human jejunal and colonic tissues. Trans-Int 3rd Annual Meeting. Apr 8-10, 2014. Montpellier, France.
2. Neve. E., Artursson, P., Ingelman-Sundberg, M., Karlgren, M. An integrated in vitro model for simultaneous assessment of drug uptake, metabolism and efflux. 5th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Jan 23, 2014. Uppsala, Sweden.

3. Baranczewski, P., Backlund, M., Mastej, M., Svensson, R., Artursson, P. The Uppsala University Drug Optimization and Pharmaceutical Profiling Facility (UDOPP). 5th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Jan 23, 2014. Uppsala, Sweden.
4. Mateus, A, Matsson P, Karlgren M, Artursson P. Impact of active uptake via OATP1B1 on intracellular unbound drug concentrations. 5th Symposium on Pharmaceutical Profiling in Drug Discovery and Development, Jan 23, 2014. Uppsala, Sweden.
5. Mateus, A, Matsson P, Artursson P. A novel methodology to predict drug binding to primary tissues using cell line homogenates. 5th Symposium on Pharmaceutical Profiling in Drug Discovery and Development, Jan 23, 2014. Uppsala, Sweden.
6. Persson, LC., Porter, CJH., Charman, WN., Bergström, CAS. Drug solubility in excipients of lipid based formulations. 5th Symposium on Pharmaceutical Profiling in Drug Discovery and Development, Jan 23, 2014. Uppsala, Sweden.
7. Andersson, S.B.E., Lindahl, A., Fagerberg, J., Ragnarsson, G., Bergström, C.A.S. Solubility Profiling for Biopharmaceutics Classification System Class 2 Compounds with Complete Absorption in Vivo. 5th Symposium on Pharmaceutical Profiling in Drug Discovery and Development, Jan 23, 2014. Uppsala, Sweden.
8. Pedersen JM, Matsson P, Bergström CA, Hoogstraate J, Norén A, LeCluyse EL, Artursson P. Early Identification of Clinically Relevant Drug Interactions with the Human Bile Salt Export Pump (BSEP; ABCB11). Society of Toxicology. Mar 23-27, 2014. Phoenix, USA.
9. Pedersen, JM, Svedberg, E, Lai, Y, Qiu, X, Norén, A, Palm, J, Hoogstraate, J and Artursson, P. Biliary Drug Excretion in Sandwich-Cultured Human Hepatocytes: Predicted from Inverted Membrane Vesicles and Targeted Proteomics. Society of Toxicology. Mar 23-27, 2014. Phoenix, USA.
10. Gaugaz, FZ., Gröer, C., Busch, D., Oswald, S., Wisniewski, J., Warpman Berglund, U., Helleday, T., Baranczewski, P., Artursson, P. Mapping Drug Transporters, Metabolizing Enzymes and Cancer Target MTH1 in Cancer Cell Lines. Gordon Research Conference Drug Metabolism. Jul 6-11, 2014. Holderness, USA.
11. Vildhede, A., Ölander, M., Wisniewski, J.R., Karlgren, M., Norén, A., Artursson, P. Global membrane protein analysis of the human liver: application in predictions of atorvastatin uptake clearance. Gordon Research Conference Drug Metabolism. Jul 6-11, 2014. Holderness, USA.
12. Wegler, C., Wikvall., Norlin, M. Effects of osteoporosis-inducing drugs on vitamin D-metabolizing enzymes in osteoblast-like cells. Vitamin D and Human Health: From the Gamete to the Grave. Apr 23-25, 2014. London, UK.
13. Karlgren, M., Vildhede, A., Ölander, M., Wisniewski, J.R., Norén, A., Artursson, P. Global membrane protein analysis of the human liver: application in predictions of atorvastatin uptake clearance. 19th North American ISSX Meeting/ 29th JSSX Meeting, Oct 19-23, 2014. San Francisco, USA.
14. Persson, L., Diesch E., Charman, W., Porter, C., Bergström, C. Prediction of drug loading in single excipients and lipid based formulations. 5th FIP Pharmaceutical Sciences World Congress. Apr 13 -16, 2014. Melbourne, Australia.

15. Persson L., Friberg A., Bergström C. Assessment of computational and experimental models for prediction of drug solubility in triglycerides. CRS Nordic Chapter, Aug 26-27, 2014. Helsinki, Finland.
16. Persson L., Friberg A., Bergström C. Assessment of computational and experimental models for prediction of drug solubility in triglycerides. AAPS Annual meeting Nov 2-6, 2014. San Diego, USA.
17. Vallianatou, T., Lodén, H., Nilsson, A., Shariagorji, M., Pereira, M., Svenningsson, P., Karlgren, M., Andrén, P.E. Blood-brain barrier drug targeting by mass spectrometry imaging in early ADME profiling. 1st International Congress: From Drug Discovery to Drug Delivery, Nov 13-15, 2014. Athens, Greece.
18. Fagerberg, J. H., Jern, E., Bergström, C.A.S., Ethanol effects on apparent solubility of poorly soluble drugs in simulated gastric fluid. 5th FIP Pharmaceutical Sciences World Congress. Apr 13 -16, 2014. Melbourne, Australia.
19. Fagerberg, J. H., Sjögren, E., Bergström, C.A.S., Concomitant intake of alcohol can increase the absorption of poorly soluble drugs administered as immediate release formulations. Physchem Forum, Apr 9-10, 2014. East Grinstead, England.
20. Fagerberg, J. H., Sjögren, E., Bergström, C.A.S., Concomitant intake of alcohol increases the absorption of poorly soluble drugs administered as immediate release formulations. CRS Nordic Chapter, Aug 26-27, 2014. Helsinki, Finland.
21. Fagerberg, J. H., Karlsson, E., Ulander, J., Hanisch, G., Bergström, C.A.S., Computational prediction of apparent solubility of lipophilic drugs in aspirated human intestinal fluid. CRS Nordic Chapter, Aug 26-27, 2014 Helsinki, Finland.
22. Fagerberg, J. H., Sjögren, E., Bergström, C.A.S., Concomitant Intake of Alcohol Increases the Absorption of Poorly Soluble Drugs Administered as Immediate Release Formulations. AAPS Annual meeting, Nov 2-6, 2014. San Diego, USA.
23. Fagerberg, J. H., Karlsson, E., Ulander, J., Hanisch, G., Bergström, C.A.S., Computational Prediction of Apparent Solubility of Lipophilic Drugs in Aspirated Human Intestinal Fluid AAPS Annual meeting, Nov 2-6, 2014. San Diego, USA.
24. Andersson, S.B.E., Lindahl, A., Fagerberg, J., Ragnarsson, G., Bergström, C.A.S. Solubility Profiling for Biopharmaceutics Classification System Class 2 Compounds with Complete Absorption in Vivo. PhysChem Forum, Apr 9– 10, 2014, East Grinstead, UK.
25. Andersson, S.B.E., Lindahl, A., Fagerberg, J., Ragnarsson, G., Bergström, C.A.S. Solubility Profiling f Biopharmaceutics Classification System Class 2 Compounds with Complete Absorption in Vivo. OrBiTo Meeting, May 12 – 14, 2014, Stevenage, UK.
26. Andersson, S.B.E., Fagerberg, J.H., Bergström, C.A.S. Small Scale Dissolution Profiling of Highly Lipophilic Compounds under Physiological Conditions. 3rd Galenus Workshop: Predicitve Dissolution Testing – News and Views, Jul 2 – 4, 2014, Greifswald, Germany.
27. Andersson, S.B.E., Fagerberg, J.H., Bergström, C.A.S. Small Scale Dissolution Profiling of Highly Lipophilic Compounds under Physiological Conditions. CRS Nordic Chapter, Aug 26-27, 2014. Helsinki, Finland.

28. Andersson, S.B.E., Lindahl, A., Fagerberg, J., Ragnarsson, G., Bergström, C.A.S. Solubility Profiling f Biopharmaceutics Classification System Class 2 Compounds with Complete Absorption in Vivo. AAPS Annual meeting, Nov 2-6, 2014. San Diego, USA.
29. Holmboe, M., Bourg, I.C. Molecular dynamics simulations of hydrated Montmorillonite, NordForsk 2014, Jan 29-31, 2014. Uppsala, Sweden
30. Holmboe, M., Fagerberg, J.H., Anwar, J., Bergström, C.A.S Lipoidal Structures present in Simulated Intestinal Fluids Modeled by Molecular Dynamics Simulations, AAPS Annual meeting, Nov 2-6, 2014. San Diego, USA

Abstracts Oral Presentation

1. Mateus, A., Matsson, P., Karlgren, M., Artursson, P. A novel methodology to measure the impact of active transport on intracellular unbound concentrations. New Perspectives in DMPK, Feb 10, 2014. London, UK
2. Karlgren, M. In vitro models for prediction of drug transport and drug metabolism. Minisymposium "Anti-HIV therapy – Let's boost your knowledge", Jan 10, 2014. Leuven, Belgium.
3. Karlgren, M. Strategies for predicting drug transport and drug metabolism. Predictive chemistry in drug discovery and development. Sep 25, 2014. Mölndal, Sweden.
4. Karlgren, M. Predictions of OATP mediated drug transport. Medical Products Agency. Nov 11, 2014. Uppsala, Sweden.
5. Lundquist, P. Improved methods for the prediction of hepatic and biliary clearance. 5th International conference on clinically relevant drug transporters. Mar 17-18, 2014. Berlin, Germany.
6. Lundquist, P. Ussing chambers for the study of nano-carrier permeability in human jejunal and colonic tissues. Trans-Int 3rd Annual Meeting. Apr 8-10, 2014. Montpellier, France.
7. Ölander, M., Treyer, A., Gaugaz, F.Z., Wong, E., Artursson, P. All Hepatocytes are not equal: Characterization of Variability in cryopreserved human Hepatocytes. GPEN 2014. Aug 27-30, 2014. Helsinki, Finland.
8. Persson L., Diesch E., Charman W., Porter C., Bergström C. Prediction of drug loading in single excipients and lipid based formulations. The Third Annual FTPT Network Meeting, Jan 29 – 31, 2014. Uppsala, Sweden.
9. Persson L., Diesch E., Charman W., Porter C., Bergström C. Prediction of drug loading in single excipients and lipid based formulations. GPEN 2014. Aug 27 - 30, 2014. Helsinki, Finland.
10. Andersson, S.B.E., Lindahl, A., Fagerberg, J., Ragnarsson, G., Bergström, C.A.S. Solubility Profiling f Biopharmaceutics Classification System Class 2 Compounds with Complete Absorption in Vivo. The Third Annual FTPT Network Meeting, Jan 29– 31, 2014. Uppsala, Sweden.

11. Bergström C.A.S. Computational Prediction of Apparent Solubility of Lipophilic Drug Molecules in Fasted State Intestinal Fluid, Pharmaceutical Sciences World Congress, Apr 13-16, 2014, Melbourne, Australia.
12. Bergström C.A.S. Solubility and Formulate-ability: Key Molecular Determinants of Developability of Ligands to Contemporary Targets. Pharmaceutical Sciences World Congress, Apr 13-16, 2014. Melbourne, Australia.
13. Bergström C.A.S. Early recognition of poor drug solubility: new in silico and in vitro tools to identify solubility issues and possible solutions through enabling formulations strategies. University of Michigan, Aug 1, 2014. Ann Arbor, USA.
14. Bergström C.A.S. Biorelevant Dissolution Profiling: A Molecular Perspective. Conference on In vivo predictive dissolution, Aug 3-6, 2014. Ann Arbor, USA.
15. Bergström C.A.S., Karlgren M., Matsson P. Pharmaceutical Profiling to Reduce, Refine, Replace (3R); Computational models predict human drug transport and disposition. Digital Health Days, Aug 25, 2014. Stockholm, Sweden.
16. Bergström C.A.S. Solubility and Formulate-ability: Key Molecular Determinants of Drug Developability. Predictive chemistry in drug discovery and development, Sep 26, 2014, Gothenburg, Sweden.
17. Holmboe, M., Fagerberg, J.H., Anwar, J., Bergström, C.A.S Computational pharmaceutics using Molecular Dynamics simulations. IMI OrBiTo F2F meeting, May 12-14, 2014 Stevenage, UK.
18. Holmboe, M., J.H., Anwar, Bergström, C.A.S. Clustering of intestinal lipids as studied by Molecular dynamics simulations. Seminar talk at Dept. of Pharm, University of Copenhagen, Oct 29, 2014. Copenhagen, Denmark
19. Holmboe, M., J.H., Anwar, Bergström, C.A.S. Clustering of intestinal lipids as studied by Molecular dynamics simulations. Aggregation and Clustering of Molecules, Workshop, Oct 30-31, 2014. Copenhagen, Denmark
20. Artursson, P. ABC-transporters in hepatic drug clearance and drug-induced liver injury (DILI). 5th symposium on pharmaceutical profiling in drug discovery and development. Jan 23, 2014. Uppsala, Sweden
21. Artursson, P. Transport proteins in hepatic drug clearance and drug-induced liver injury (DILI). ADME & Predictive Toxicology. Feb 18-19, 2014. Barcelona, Spain.
22. Artursson, P. Ulla lecturer: Transporters modulating drug disposition. Mini-symposium ADME profiling. 12 Mar, 2014. Leuven, Belgium.
23. Artursson, P. ABC-transporters in hepatic drug clearance and drug induced liver injury (DILI) – *in vitro* models and *in vivo* predictions. Clinically relevant drug transporters. Mar 17-18, 2014. Berlin, Germany.
24. Artursson, P. Prediction of the impact of transport mechanism on intestinal drug absorption. CRS Nordic Chapter Meeting. Aug 26, 2014. Helsinki, Finland
25. Artursson, P. New cell based approaches for better predictions of drug target and off target efficacy. GPEN 2014, Aug 27-30, 2014, Helsinki, Finland
26. Artursson, P. Prediction of the impact of transport mechanism on intestinal drug absorption. Gattefosse meeting. 11-13 Sept, 2014, Mas Bellile, France.

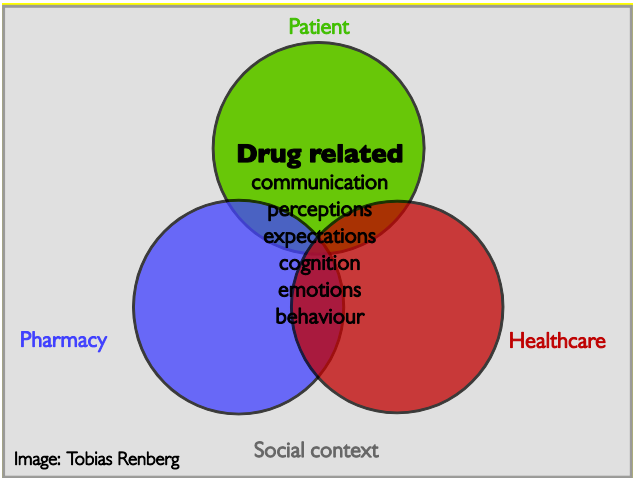
27. Artursson, P. *In vitro* and *in vivo* models for assessment of oral drug absortion. SF Nano Workshop, Oct 2, 2014. Porto, Portugal.
28. Artursson P, Karl Johan Öbrink lecture. Transport proteins: integral membrane proteins that determine drug efficacy. Nov 17, 2014. Uppsala, Sweden.
29. Matsson, P. Intracellular drug exposure and unbound drug concentrations. Medical Products Agency. Nov 11, 2014. Uppsala, Sweden,

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 Kälvemark 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 Kälvemark 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 Kälvemark 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 Kälvemark 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 Kälvemark 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 2014

Ida Bergström, 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 2014

1. Frisk, P, Kälvemark-Sporrong, S and Wettermark, B. Selection bias in pharmacy-based patient surveys. *Pharmacoepidemiology and Drug Safety*, 2014, 23 (2), 128.
2. 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.
3. Olsson, E, Ingman, P, Ahmed, B and Kälvemark-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 Kälvemark Sporrong, S. Communications Training in Pharmacy Education, 1995-2010. *American Journal of Pharmaceutical Education,* 2013, 77 (2), 36.
3. Rönnbäck, E, Kälvemark 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.

Publications, reviews and book chapters 2012

1. Carlsson, JR, Renberg, T and Kälvemark Sporrong, S. Drug experts of the future, today?: Depiction of the pharmacist profession in Swedish professional and lay print media. *Research in Social and Administrative Pharmacy*, 2012, 8 (2), 133.
2. Fagerlind, H, Kettis, Å, Bergström, I, Glimelius, B and Ring, L. Different perspectives on communication quality and emotional functioning during routine oncology consultations. *Patient Education and Counseling*, 2012, 88 (1), 16.
3. Nordén-Hägg, A, Kettis Lindblad, Å, Ring, L and Kälvemark Sporrong, S. Experiences of a nationwide web-based system: reporting dispensing errors in Swedish pharmacies. *International Journal of Pharmacy Practice.* 2012, 20 (1):25.
4. Nordén-Hägg, A, Kälvemark Sporrong, S and Kettis Lindblad, Å. Exploring the relationship between safety culture and reported dispensing errors in a large sample of Swedish community pharmacies. *BMC Clinical Pharmacology & Toxicology,* 2012, 13:4.
5. Nordén Hägg, A, Shamoon, M and Kälvemark Sporrong, S. Deregulation of nonprescription medicines in Sweden-A look at the control system. *Research in Social and Administrative Pharmacy*, 2012, 8 (6), 567.
6. Olsson, E and Kälvemark Sporrong, S. Pharmacists experiences and attitudes regarding generic drugs and generic substitution: Two sides of the coin. *International Journal of Pharmacy Practice*, 2012, 20 (6), 377.
7. Pettersson, K, Carlsson, G, Holmberg, C and Kälvemark Sporrong, S. Cost identification of Nordic FLIRI, Nordic FLOX, XELIRI and XELOX in first-line treatment of advanced colorectal cancer in Sweden: A clinical practice model approach. *Acta Oncologica*, 2012, 51 (7), 840.
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Pharmaceutical Physical Chemistry

Professor Martin Malmsten

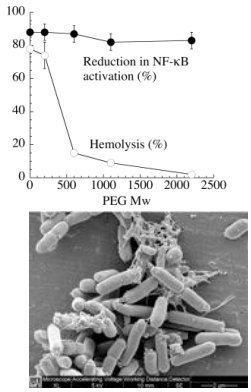
Within the group for Pharmacrutical Physical Chemistry, research is performed on polymer and lipid systems as tools for discovery, optimization, and delivery of drugs, with particular focus of peptide and protein drugs, and antimicrobial and anti-inflammatory drugs in particular. The research is characterized by broad collaborations to span the range from basic biophysical and physicochemical investigations, to studies of antimicrobial and anti-inflammatory 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, and surfactants, iv) protein sorting in polyelectrolyte networks, and v) polymer-based nanoparticulate drug delivery systems.

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, and is currently subject of further clinical trials. Exemplifying activities during 2014, 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 selecticity improved. Through this, conditions can be found, at which the PEGylated peptide displays simultaneously efficient antimicrobial affects 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.



AMP PEGylation?

⇩ Antimicrobial effect
⇩ Toxicity
⇧ Selectivity
⇨ Anti-endotoxic effect

Project area 2: Interaction between microgels and proteins/peptides

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

In this project area we investigate microgels 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. In a series of studies, we have investigated effects of peptide composition (charge, hydrophobicity and their respective distributions), length, secondary structure, and cyclization. During the last two 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. During 2014, we also initiated two new PhD projects, 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.

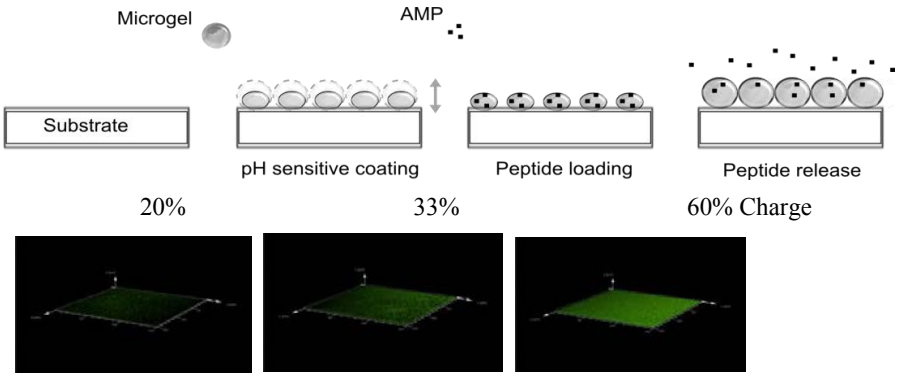


Figure. Schematic illustration of microgel coating of biomaterials, as well as subsequent peptide loading (top). Shown also (bottom) are confocal microscopy images with labeled peptide loaded to surface-bound microgels of different charge density.

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. In particular the results clarify the conditions required for the appearance of discrete gel volume transitions, induced by both core/shell separation and gel bulk instability.

Project area 4: Protein sorting in polyelectrolyte networks

Prof Per Hansson, Claes Jidheden

In this recently started 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.

Project area 5: Nanoparticulate drug delivery systems

Prof Martin Malmsten, Stefano Colombo, Lise-Britt Wahlberg

During 2014, we run a set of research activities within the area of polymer-based nanoparticulate drug delivery systems. An example of these activities was the establishment of 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 preciptation by sub- or supercritical CO_2. 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 bioavalilability *in vivo* was demonstrated for male beagle dogs following oral administration of gelatin capsules containing the hybrid nanoparticles, where a 730% increase in the $AUC_{0\text{-}24hr}$ was observed compared to the benchmark formulation. In two follow-up activities, we have 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 benaficial effects have been further clarified. In a second line of research, we intitiated during 2014 studies on 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.

Members of the group during 2014

Martin Malmsten, Professor

Per Hansson, Professor

Anders Ericsson, Associate professor

Günter Siegel, Visiting professor

Jonas Gernandt, PhD, Senior lecturer

Stefano Colombo, Researcher

Claes Jidheden, PhD Student

Randi Nordström, PhD Student

Lina Nyström, PhD Student

Shalini Singh, PhD Student

Lise-Britt Wahlberg, Technician

Ronja Widenbring, PhD Student

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.
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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.
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Funding

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

Doctoral dissertation

Presentations at symposia and congresses 2014

1. Widenbring, R., Bysell, H., Frenning, G., and Malmsten, M. Factors affecting enzymatic degradation in peptide/protein-loaded microgels. 20th SIS, Coimbra, 22-27 June, 2014. Invited lecture.
2. Malmsten, M. Development of scientific communication – a journal editor's perspective. Reaxys – inspiring chemistry, Grindelwald, 21-22 September, 2014. Invited lecture.
3. Malmsten, M. Membrane and lipopolysaccharide interactions of antimicrobial and anti-inflammatory peptides. COST iPROMEDAI Meeting, Porto, 23-31 October, 2014. Invited lecture.
4. Malmsten, M. Novel opportunities of nanoparticle-based delivery systems for biomacromolecular drugs – an introductory overview. Nanomedicine, Malmö, 9-10 October, 2014. Plenary lecture.
5. Claes Jidheden and Per Hansson. Single microgels in core/shell equilibrium: A novel method for limited volume studies. Realizing reformulation. A symposium on surface and materials chemistry, Lund, 23-25 oktober 2014. Poster.
6. Lina Nyström. Peptide-loaded microgels as antimicrobial surface coatings. Realizing reformulation. A symposium on surface and materials chemistry, Lund, 23-25 oktober 2014. Poster.

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 research programme of the group consists of a series of projects that are run by four project groups, each led by a principle investigator. In the Table below, an overview of the projects groups and the projects run are given and the projects are subsequently briefly described.

Overview of research programme and projects 2014

Project groups	*Projects*
Pharmaceutical materials science	(a) Properties of amorphous composites (b) Prediction of disordering propensity of solids
Pharmaceutical physics	(a) Experimental studies of single particles under confined conditions (b) Mechanistic models for the interaction between particles under confined conditions (c) Distinct-particle simulations of confined compression/compaction
Pharmaceutical technology	(a) Formulation tools for characterizing particle mechanics and powder compactibility (b) Multiscale structure-property relationships for granular solids (c) Mechanical amorphisation of particles
Drug administration	(a) Formulations for mucosal and transdermal drug delivery

Project area 1: Pharmaceutical materials science

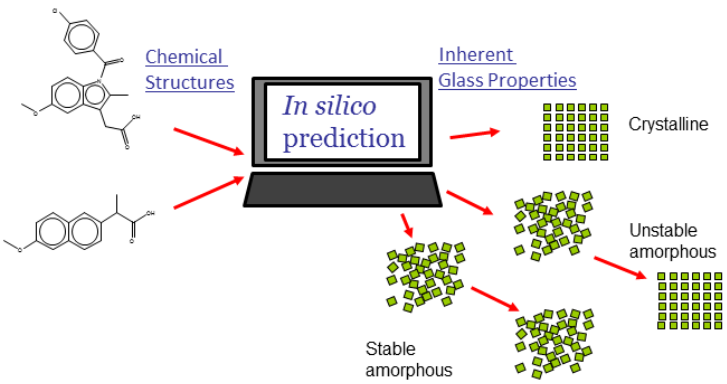
Principle investigator: Denny Mahlin

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 2014, 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 tranformations of the formed composite in terms crystallization, particle agglomeration behaviour and mechanical properties.



(b) Prediction of disordering propensity of solids

Different materials have different propensity to become amorphous when exposed to manufacturing operations such as drying, mixing and compaction. By statistical modeling we are developing prediction tools which give us the opportunity to predict the disordering potential and amorphous stability of drug-like solids in the dry state and in aqueous dispersions. Since disordering leads to large changes in material properties,

predictions could help alerting problematic compounds that are intended to be included in a formulation. Also it can highlight the possibilities to utilize amorphization to improve material properties, such as poor solubility. The overall aim is to better understand the molecular properties that govern the ability of a solid material to become a stable amorphous solid, both during storage and dissolution.

Project area 2: Pharmaceutical physics

Principle 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 2014, the following projects have been running within the group:

(a) Experimental studies of single particles under confined conditions

An 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/compaction

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.

Project area 3: Pharmaceutical technology

Principle 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 aand 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 2014, the following projects have been running within the group:

(a) Formulation tools for characterizing particle mechanics and powder compactibility

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) Multi-scale structure-property relationships for 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) Mechanical amorphisation of particles

It is today well established that a particulate solid may undergo a transformation from a crystalline to an amorphous 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 amorphise the particles, causing alterations in the chemical and physical properties of the solid. We intend to investigate the amorphisation of particles during powder flow and the type of inter-particulate contact processes that may cause amorphisation. Furthermore, we wish to identify the mechanism on the molecular scale that is involved in the disordering of a solid during powder flow.

Project area 4: Drug administration

Principle investigator: Erik Björk

The release of the drug from a pharmaceutical formulation is often of great importance for the therapeutic effect. Understanding of the mechanisms controlling the release rate as well as knowledge on how to alter the release rate from different formulations are dominant aspects of the development of a dosage form.

During 2014, the following project has been running within the group:

(a) Formulations for mucosal and transdermal drug delivery

The objective of the project is to develop new formulation concepts for mucosal and skin administration of drugs, primarily by the nasal and transdermal route. Both low molecular drugs and peptides are in focus. The mechanistic understanding of the release of drugs from the formulation and its effect on the mucosal epithelium that may alter the absorption are parameters that are studied. Current examples are gel formulations with drugs included in vesicles with surfactants to alter the release. These systems can be used for application on different mucosa and also on the skin.

Members of the group during 2014

Göran Alderborn, Professor

Erik Björk, Senior lecturer

Ragnar Ek, Associate professor

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

Lena Strindelius, Senior lecturer

Publications, reviews and book chapters 2014

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8. Frenning G. Modelling implications. Pan European Networks: Science & Technology 13, 202–203 (2014).

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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. *Internation Journal of Pharmaceutics,* 2013, 453 (2), 295.

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1. Dew, N, Edwards, K, Eriksson, J, Edsman, K and Björk, E. Gel formulations containing catanionic vesicles composed of alprenolol and SDS: effects of drug release and skin penetration on aggregate structure. *Colloids and Surfaces B: Biointerfaces*, 2012, 89, 53.
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Funding

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

Presentations at symposia and congresses 2014

1. Frenning, G. An extended truncated-sphere model for DEM simulations of confined powder compression. Particulate Processes in the Pharmaceutical Industry IV, Potsdam, Germany, September 14 – 18, 2014.
2. Jonsson H. Evaluation of experiments employing confined compression of single granules. Particulate Processes in the Pharmaceutical Industry IV, Potsdam, Germany, September 14 – 18, 2014.
3. Hellrup J., Alderborn, A. and Mahlin, D. Recrystallization of amorphous lactose in spray-dried nanocomposites. PBP World Meeting, Lissabon, Portugal, March 30 – April 3, 2014.
4. Mahlin, D. Prediction of glass formation and stability of drugs. APS - Amorphous By Design 2014, Bradford, England, April 28 – 29, 2014.
5. Mahlin, D. Glass Property Prediction From Molecular Structure. APS - Amorph2014, Cambridge, England, July 14 – 16, 2014.

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.

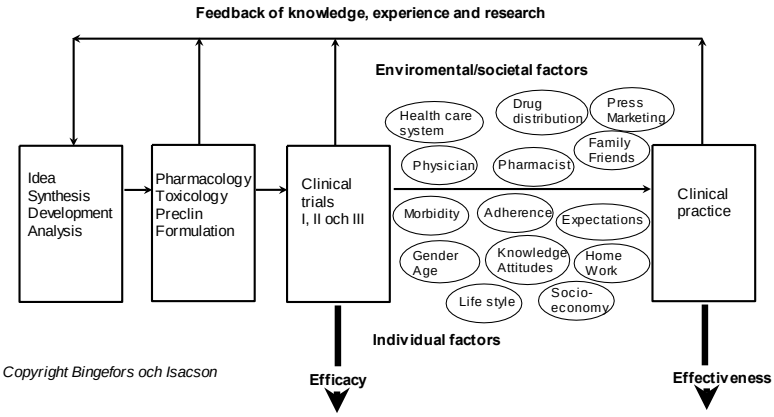

Figure 1. The development of drugs and efficacy/effectiveness of drug treatment

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. During the year Lena Thunander Sundbom successfully presented her Licentiate dissertation. She is continuing her PhD-project with a study on self-reported depression and the prescribing of antidepressants from a gender perspective.

Members of the group during 2014

Dag Isacson, Professor

Kerstin Bingefors, Associate professor

Helena Wennborg, MD PhD

Lena Thunander Sundbom, Licentiate, PhD student

Publications, reviews and book chapters 2014

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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.
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Publications, reviews and book chapters 2012

1. Thunander Sundbom, L and Bingefors, K. Women and men report different behaviours in, and reasons for medication non-adherence: a nationwide Swedish survey. *Pharmacy Practice,* 2012, 10, 207.

Doctoral dissertation

Thunander Sundbom, L. The influence of gender and psychological distress to prescribed medication. Licentiate thesis 45, 2014.

Other information

Dissertations

1. Fagerberg, J. Experimental and computational predictions of drug solubility in human gastrointestinal fluids. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 187, 2014.
2. Thunander Sundbom, L. The influence of gender and psychological distress to prescribed medication. Licentiate thesis 45, 2014.

Awards 2014

Bergström, C, Karlgren, M, Matsson, P. The 2014 Nordic Research Prize for Alternatives to Animal Experiments, from the Swedish Foundation for Research without Animal Experiments, Alternativfondet (Denmark) and the Juliana von Wendt Foundation (Finland).

Matsson, P. Assistant Professor, Disciplinary Domain of Medicine and Pharmacy, Uppsala University.

Fellowships

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

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