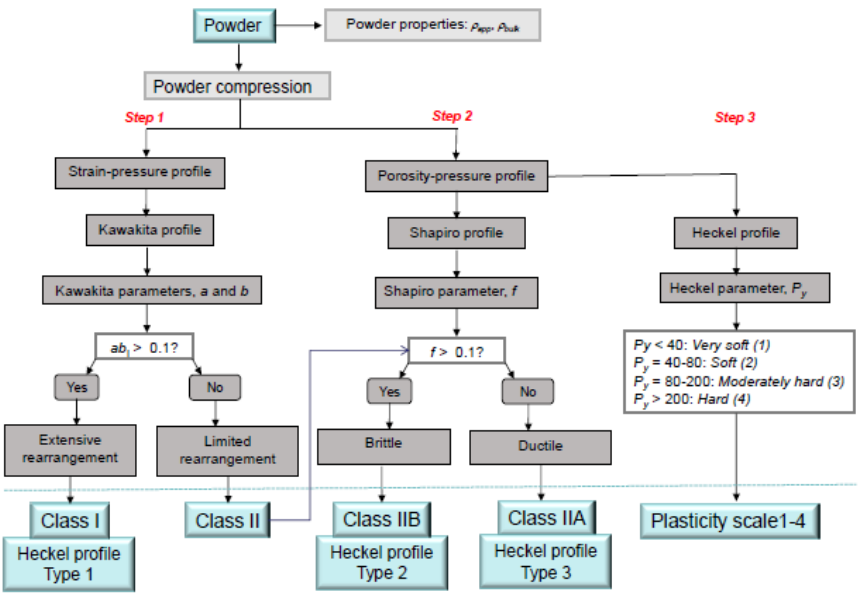
UPPSALA UNIVERSITET

Department of Pharmacy

ANNUAL REPORT 2012



Department of Pharmacy

ANNUAL REPORT 2012

Preface

Welcome to the Annual Report of the Department of Pharmacy at Uppsala University. Besides the chairman´s report, the repoprt contains brief summaries from the research groups, including their publications and other achievements. 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 collaboration within our research and teaching programs, or through the provision of funding. I look forward to further fruitful relationships during the coming year.

Uppsala 2013-03-01

Martin Malmsten

Chairman, Department of Pharmacy

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Chairman´s report

Research

Our research carried out at the department is centered around three aspects of the Pharmacy discipline, 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* (lead by Prof Hans Lennernäs) studies the interaction between drugs and biological processes, e.g., membrane transport and metabolism, and develops new concept formulations for drug delivery.
- *Drug Delivery* (lead by Prof Per Artursson) 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* (lead by Dr Sofia Kälvemark-Sporrong) 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* (lead by Prof Martin Malmsten) develops design principles for pharmaceutically relevant systems at a molecular and colloidal scale.
- *Pharmaceutics* (lead by Prof Göran Alderborn) studies pharmaceutical formulation and manufacturing.
- *Pharmacoepidemiology and Pharmacoeconomics* (lead by Prof Dag Isacson) 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 PhDs in our disciplines in academic, industrial, regulatory, and pharmacy sectors, the department maintains a high ambition regarding PhD education. The work of our PhD students represents a significant contribution 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 training of PhDs 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.

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, and 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 2012, personnel situation at the department has been stable from a personnel turnover perspective. However, for staff working on the practice period within our programmes, the year has brought continued uncertainties and hard work related to the re-regulation of the Swedish pharmacy monopoly. Together, we have therefore worked hard, both within the department and together with the Faculty of Pharmacy, to find solutions to these problems in order to provide a better service to our students, and a better working environment to our staff involved in these activities. We are happy to report that this has resulted in a strengthening of the organization at the Faculty level to handle placements, which will hopefull ease the situation considerably.

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 to strong, and has during 2012 allowed for strategic investments in research instrumentation, as well as research personnel. The varying funding for the undergraduate teaching does, however, remain a problem for the department, as well as for the Faculty of Pharmacy. Together with the other departments of the Faculty, 2012 therefore saw initiation of novel activities to further increase quality of our research activities, and to modernize the content and structure of our programmes.

Revenues to the Department of Pharmacy 2012 (kSEK)

University funding - Undergraduate teaching	17 996
Contract teaching	296
University funding - Research and post-graduate teaching	22 522
Research grants	8 936
Commissioned research	2 807
Total	52 557

Organization and personnel

Organization

Chairman

Martin Malmsten

Deputy chairman

Per Artursson

Department board

Martin Malmsten, chairman
Göran Alderborn, teacher representative
Per Hansson, teacher representative
Sofia Kälvemark Sporrong, teacher representative
Christin Magnusson, teacher representative
Christel Bergström, teacher representative, deputy
Hans Lennernäs, teacher representative, deputy
Johan Gråsjö, representative for technical/administrative personnel
Göran Ocklind, representative for technical/administrative personnel, deputy
Jonas Fagerberg, graduate student representative
Ronja Månsson, graduate student representative
Anna Vildhede, graduate student representative, deputy
Elin Andersson, student representative (Jan-June)
Marcus Wanselius, student representative (July-Dec)
Eva Nises Ahlgren, secretary

Director of administration

Eva Nises Ahlgren

Director of graduate studies

Per Artursson

Directors of undergraduate studies

Kerstin Bingefors
Anders Ericsson
Sofia Kälvemark Sporrong
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, Associate professor
Per Hansson, PhD, Professor in Physical Chemistry
Dag Isacson, PhD, Professor in Pharmacoepidemiology
Lars Knutson, PhD, Visiting professor
Sofia Kälvemark Sporrong, PhD, Senior lecturer
Hans Lennernäs, PhD, Professor in Biopharmaceutics
Christin Magnusson, BSc, Lecturer
Denny Mahlin, PhD, Assistent professor
Martin Malmsten, PhD, Professor in Pharmaceutical Physical Chemistry
Ulf Norinder, PhD, Adjunct professor
Erika Olsson, MSc, Research assistant
Lena Ring, PhD, Associate professor, Adjunct senior lecturer
Günter Siegel, PhD, Visiting professor
Erik Sjögren, PhD, Senior lecturer
Jannike Stenlund, MSc, Lecturer
Lena Strindelius, PhD, Senior lecturer
Helena Wennborg, MD PhD, Guest lecturer

PhD Students	**Supervisors**
Emelie Ahnfelt	Hans Lennernäs
Sara Carlert	Hans Lennernäs

Ilse Dubbelboer	Hans Lennernäs
Jonas Fagerberg	Christel Bergström
Hanna Fagerlind	Lena Ring
Jonas Gernandt	Per Hansson
Mina Heidarian Höckerfelt	Göran Alderborn
Joel Hellrup	Denny Mahlin
Claes Jidheden	Per Hansson
Elsa Lilienberg	Hans Lennernäs
Foad Mahmoodi	Göran Frenning
André Mateus	Per Artursson
Ronja Månsson	Martin Malmsten
Samaneh Pazesh	Göran Alderborn
Jenny Pedersen	Per Artursson
Ann-Sofie Persson	Göran Frenning
Linda Persson	Christel Bergström
Shalini Singh	Martin Malmsten
Helena Thörn	Hans Lennernäs
Anna Vildhede	Per Artursson
Kristin Wisell	Sofia Kälvemark Sporrong

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

Research scientists

Maria Backlund, PhD
Pawel Baranczewski, PhD
Jenny Felth, PhD
Luca Fenu, PhD
Mathilde Hedlund Lindberg, PhD
Maria Karlgren, PhD
Lucia Lazorova, PhD
Patrik Lundquist, PhD

Malin Masterton, PhD
Pär Matsson, PhD
Josefina Nordström, PhD
Christian Pedersen, PhD
Erik Sjögren, PhD
Richard Svensson, PhD

Administrative and technical staff

Johan Gråsjö, MSc
Eva Lide
Maria Mastej, BSc
Eva Nises Ahlgren, BSc
Göran Ocklind, PhD
Birgitta Rylén
Linda Strandenhed
Elin Svedberg, MPharm
Lise-Britt Wahlberg
Ulla Wästberg Galik

Mini-biographies of permanent staff (January 1st 2013)

Alderborn, G.

Research interests

Göran Alderborns research work centers on the technology and materials science of solid dosage forms. Current research projects focus on the characterization of mechanical properties of powders, the engineering of granular materials and the properties of amorphous solids.

Examples of current commitments

- Dean of the Faculty of Pharmacy, Uppsala University
- Chairman of the Faculty of Pharmacy Committee
- Chairman of the Appointment Committee of the Faculty of Pharmacy
- Member of the Board of the Disciplinary Domain of Medicine and Pharmacy
- 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, accumulation, metabolism and elimination of drugs and drug-like molecules is studied. During 2012, our collaborative platform for pharmaceutical profiling and drug optimization, UDOPP, was expanded, both with regard to staff and to the number of collaborative projects.

Examples of current commitments

- Deputy Head of Department of Pharmacy, Uppsala University
- Deputy Head of the Committee for postgraduate studies at the Faculties of Pharmacy and Medicine
- Director of Graduate Studies at the Department of Pharmacy

- 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
- Member of the Scheele award committee
- Honorary Professor at the University of Queensland, Brisbane, Australia

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 product 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 Department of Pharmacy, Uppsala University
- Member of the Board of the Controlled Release Society Nordic Chapter
- Member of organizing committee for conferences, exemplified by “Drug solubility- a challenge in pharmaceutical development” arranged by the Swedish Association for Pharmaceutical Sciences and the Symposium on Pharmaceutical Profiling arranged by the Department of Pharmacy every second year.

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 of the Board of the Department of Pharmacy, Uppsala University
- Member of the Gender Equality Committee at the Department of Pharmacy
- Member of the Editorial Board of ISRN Pharmaceutics
- Reviewer for more than 20 international journals
- Member of the organizing committee for conferences such as *Drug Processing and Delivery*, Södertälje, Sweden, November 12-14, 2012.

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 Board of the Department of Pharmacy, Uppsala University
- Deputy member of the Committee of Education at the Faculty of Pharmacy, Uppsala University
- Member of the structure group for the development of new pharmacist programs at Uppsala University

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
- Research Director, Pharmacoepidemiology and Pharmacoeconomics, Dept of Pharmacy

Karlgren, M.

Research interests

Maria Karlgren works in the area of ADME and predictive pharmacokinetics and 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. Current research includes the influence of protein expression levels on hepatic drug transport and drug-drug interactions, simultaneous assessment of hepatic drug uptake, metabolism and efflux *in vitro*, and models for improved predictions of CNS drug delivery.

Examples of current commitments

- Focus area expert in *in vitro* drug transport, Uppsala University Drug Optimization and Pharmaceutical Profiling Platform
- Member of the organizing committee of the Symposium on Pharmaceutical Profiling arranged every second year by the Department of Pharmacy

Kälvemark Sporrong, S.

Research interests

Sofia Kälvemark Sporrong's research interests are professional ethics, pharmacy practice research, and pharmaceutical policy research. Current research deals with pharmacy policy, safety culture within pharmacy, the pharmacist professions, and patients' view on research and researchers.

Examples of current commitments

- Member of the Steering Committee of the Special Interest Group in Social Pharmacy, Swedish Academy of Pharmaceutical Sciences
- Chair, Association of Women Researchers in Uppsala
- Member of the Board of Carl G and Lilly Lennhoff Foundation
- Member of the Board of Actavis Grant Committee
- Member of the Board of the Department of Pharmacy, Uppsala University
- Member of the election committee for the pharmaceutical faculty at Uppsala University

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.

Examples of current commitments

- Member of the board Uppsala Clinical Reserach Center (UCR), Uppsala University
- Member of the Senate at Uppsala University
- Member of the election committee for the pharmaceutical faculty at 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 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)
- Chairman for the World conference on Drug Absorption and Drug Delivery arranged by European Federation for Pharmaceutical Sciences in Uppsala, June 2013

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

- Member of the The Svedberg seminar series committee, BMC
- Member of the Board of Farmacins Alumnförening, Department 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 Board of YKI, Ytkemiska Institutet AB
- Editor for the Journal of Colloid and Interface Science
- Section editor for Current Opinion of Colloid and Interface Science
- Member of the Editorial Board of ISRN Biochemistry
- 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

- Focus Area Expert in Computational Chemistry, Uppsala University Drug Optimization and Pharmaceutical Profiling Platform
- Member of the International Transporter Consortium Task Force on Intracellular Drug Concentrations
- Member of the organizing committee for the Symposium on Pharmaceutical Profiling arranged every second year at the Department of Pharmacy

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. In all cases the ongoing projects are driven by an obvious clinical need. An innovative, cutting edge and multi-disciplinary collaboration using mainly clinical models will include research teams from: pharmaceutical technology, material science, biopharmaceutics and pharmacokinetics, drug metabolism, toxicology, oncology, gastroenterology, endocrinology, urology and regulatory science. All four 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. Focal controlled 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 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 focal controlled 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 two start-up companies that has developed a novel oral replacement therapy (www.duocort.com) for Addison disease and the development of focal drug treatment of localised prostate cancer (www.liddspharma.com). The oral modified release product, Plenadren®, was approved by EMA in July 2011 and sold to Viropharma Inc., USA.

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

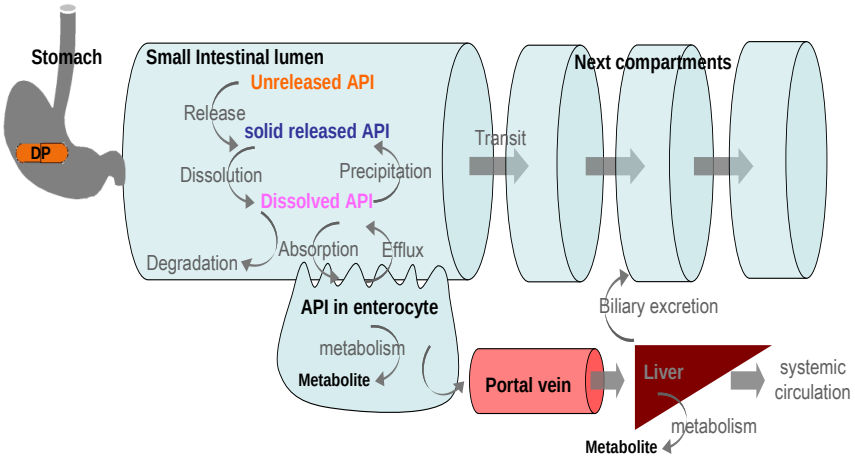

Figure 1. OrBiTo is new Eurpean project within the IMI programme in the area oral biopharmaceutics tool that include nine universities, one regulatory agency, one non-profit research organisation, three SMEs together with the twelve pharmaceutical companies (http://www.imi.europa.eu/content/orbito). 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 2012

Hans Lennernäs, Professor

Bertil Abrahamsson, Professor in industrial biopharmaceutics

Lars Knutson, Professor in clinical biopharmaceutics

Erik Sjögren, Research scientist

Emelie Ahnfelt, PhD Student

Sara Carlert, PhD Student

Ilse Dubbelboer, PhD Student

Elsa Lilienberg, PhD Student

Helena Thörn, PhD Student

Publications, reviews and book chapters 2012

1. Abrahamsson, B. The Biowaiver Monographs: the vision of the pharmaceutical industry. In FIP Biowaiver centennial, book ed JB Dressman, 2012.
2. Borde, AS, Karlsson, EM, Andersson, K, Björhall, K, Lennernäs, H and Abrahamsson, B. Assessment of enzymatic prodrug stability in human, dog and simulated intestinal fluids. *European journal of pharmaceutics and biopharmaceutics*, 2012, 80 (3), 630.
3. Carlert, S, Åkesson, P, Jerndal, G, Lindfors, L, Lennernäs, H and Abrahamsson, B. In Vivo Dog Intestinal Precipitation of Mebendazole: A Basic BCS Class II Drug. *Molecular Pharmaceutics*, 2012, 9 (10), 2903.
4. Dahan, A, Lennernäs, H and Amidon, G. The Fraction Dose Absorbed, in Humans, and High Jejunal Human Permeability Relationship. *Molecular Pharmaceutics*, 2012, 9 (6), 1847.
5. Di, L, Artursson, P, Avdeef, A, Ecker, GF, Faller, B, Fischer, H, Houston, JB, Kansy, M, Kerns, EH, Kraemer, SD, Lennernäs, H and Sugano, K. Evidence-based approach to assess passive diffusion and carrier-mediated drug transport. *Drug Discovery Today*, 2012, 17 (15-16), 905.
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1. Bergman, E, Hedeland, M, Bondesson, U and Lennernäs, H. The Effect of Acute Administration of Rifampicin and Imatinib on the Enterohepatic Transport of Rosuvastatin *In Vivo. Xenobiotica*, 2010, 40 (8), 558.
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Doctoral dissertations

1. Thörn, H. First-pass intestinal metabolism of drugs: Experiences from in vitro, in vivo and simulation studies. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 153, 2012.
2. Carlert, S. Investigation and prediction of small intestinal precipitation of poorly soluble drugs: A study involving *in silico, in vitro* and *in vivo* assessment. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 164, 2012.

Presentations at symposia and congresses 2012

1. Abrahamsson, B. AAPS Workshop on Oral Bioperformance and 21st Century Testing Chicago 2012.

2. Lennernäs, H. Drug absorption, first-pass extraction bioavailability and pharmaceutical development of oral modified release (MR) hydrocortisone (cortisol). 8 February, Läkarföreningen, Göteborgs Universitet.
3. Lennernäs, H. Successful Drug Delivery of future drugs require improved understanding of dissolution, transit and permeability. 9 February, Drug delivery symposium, Helsinki.
4. Lennernäs, H. In Vivo Methods to Assess Intestinal and Hepatobiliry Transporter-Mediated Drug-Drug Interactions, International Transporter Consortium Workshop 2, Annual of meeting of Clinical Pharmacology and Therapeutics, Washington, 6-9 March.
5. Lennernäs, H. Modulations and optimization of absorption models, European Drug Absorption Network, 25-26 March, Leuven.
6. Lennernäs, H. The Role of Passive Diffusion and Carrier-Mediated Transport in the Intestinal Drug Absorption Process. XXIInd International Symposium on Medicinal Chemistry, which will take place in Berlin, Germany on September 2-6.
7. Lennernäs, H. Oral modified drug delivery: the importance of regional aspects on dissolution, permeability and metabolism, Pharmaceutical Profiling of Drugs, September 26, Uppsala.
8. Lennernäs, H. Successful delivery of future drugs. Drug Delivery and pharmaceutical chemistry. Orion Pharma, October 4, Helsinki.
9. Lennernäs, H. In vivo and computational biopharmaceutical aspects of two drug absorption processes: precipitation and intestinal permeability. American Association Pharmaceutical Science, October 13, Chicago.
10. Lennernäs, H. Experience in Pre-clinical ADME Models to Predict Clinical Outcome: Lessons from the Past 25 Years. American Association Pharmaceutical Science, October 15, Chicago.
11. Lennernäs, H. Local drug delivery in the treatment of liver and prostate cancer. Toronto University, Department of Pharmaceutical Science, October 19.
12. Lilienberg, E. Improved Pharmacokinetic Understanding of Two Formulations for Intra-arterial Local Injection into the Liver - Liver Cancer Treatment Optimization Project (LiCTOP). Department day. Oct 9, 2012. Uppsala, Sweden.
13. Lilienberg, E, Ebeling Barbier, C, Nyman, R, Hedeland, M, Bondesson, U, Axén, N and Lennernäs, H. Poster presentation. Local and sustained release in the treatment of primary liver cancer? Pharmacokinetic understanding of two formulations for intra arterial injection. AAPS annual meeting and exposition. Oct 16, 2012. Chicago, USA.
14. Lilienberg, E, Ebeling Barbier, C, Nyman, R, Hedeland, M, Bondesson, U, Axén, N and Lennernäs, H. Poster presentation. Improved Pharmacokinetic Understanding of Two Formulations for Intra-arterial Injection. CRS Australian chapter - Drug Delivery Australia. Nov 26-27, 2012. Melbourne, Australia.
15. Lilienberg, E, Ebeling Barbier, C, Nyman, R, Hedeland, M, Bondesson, U, Axén, N and Lennernäs, H. Poster presentation. Improved Pharmacokinetic Understanding of Two Formulations for Intra-arterial Injection. GPEN. Nov 29-30, Dec 1, 2012. Melbourne, Australia.

16. Sjögren, E, Westergren, J,Grant, I, Lindfors, L, Lennernäs, H, Abrahamsson, B and Tannergren, C. Poster presentation. In Silico Predictions of Oral Drug Absorption using GI-Sim. 2012 AAPS Annual Meeting and Exposition, Chicago, Michigan, USA.
17. Sjögren, E. Poster presentation. Increased Understanding of the Systemic Bioactivation of the Double Pro-drug Ximelagatran in Pigs through Physiologically Based Pharmacokinetic Modeling. 2012 AAPS Annual Meeting and Exposition, Chicago, Michigan, USA.
18. Sjögren, E, Svanberg, P and Kanebratt, K. Poster presentation. Optimized Experimental Design for the Estimation of Enzyme Kinetic. 2012 AAPS Annual Meeting and Exposition, Chicago, Michigan, USA.
19. Sjögren, E, Tammela, T, Lennernäs, B, Malmsten, L, Axen, N and Lennernäs, H. Poster presentation. A Semi-physiological Biopharmaceutical Model for Simulation and Prediction of 2-hydroxyflutamide Concentrations in Plasma and Prostate Tissue in Prostate Cancer Patients following Local Administration of an Injectable Depot Formulation. 2012 AAPS Annual Meeting and Exposition, Chicago, Michigan, USA.
20. Sjögren, E, Hedeland, M, Bondesson, U and Lennernäs, H. Poster presentation. Verapamil Affects the Pharmacokinetics and the Hepatic Disposition of Fexofenadine in Pigs. 2012 AAPS Annual Meeting and Exposition, Chicago, Michigan, USA.

Patents and patents applications

15 patents and patens application in total.

Drug Delivery

Professor Per Artursson

The research in drug delivery is focused on predictive pharmacokinetics (ADMET) and biopharmaceutics (drug formulation, solubility and dissolution). In the ADMET area, the role of drug transporting proteins at cellular barriers is of particular interst. These integral membrane proteins determine the uptake, intracellular accumulation, metabolism and elimination of drugs.

During 2012, a new advanced cell culture model for studies of bile clearance and drug-induced liver injury mediated by bile acids was developed in collaboration with the Hamner Institute, NC, fig.1. In this model, primary human hepatocytes are grown under special conditions that allow the development of bile canaliculi. Further, two comprehensive studies focusing on hepatic uptake transporters were published. In one of these, 225 compounds were investigated for inhibition of the three important organic anion polypeptide transporters, OATP1B1, OATP1B3 and OATP2B1 expressed in human liver. Both general and specific inhibitors were identified for the different transporters. In addition, in collaborations with the Max Planck Institute and Pfizer on global and quantitative proteomics, respectively, we were able to predict the maximal transport activity of individual drug transporting proteins in the human liver, an organ that for ethical reasons is inaccessible to sampling in humans. The significance of drug-drug interactions with OATP transporters that transport many essential drugs, including statins, could also be predicted. Follow up studies are now ongoing, investigating the significance of other hepatic transport proteins as well as factors contributing to variability in their expression and function.

During the last year we also deviced our first integrated cell model where the interplay between drug transport and drug metabolism can be studied. This unique and flexible model is based on a cell line without significant background of endogenous transporters or enzymes, in which important drug transporters and drug metabolizing enzymes are co-expressed. The most complex model available today is introduced expressing five proteins. This model has been evaluated with essential drugs such as statins and has also been used for evaluation of novel drug candidates within UDOPP.

In addition, we continued the development of models for determination and prediction of intracellular unbound drug concentrations in cultured cells. The first publication resulting from this line of research was submitted. Here we define chemical properties of drugs that determine the extent of intracellular binding, and show that drug binding in easily grown cell lines is highly predictive of that in more complex primary cell cultures such as human hepatocytes. Additional studies were initiated, aiming to determine the predictive value of unbound versus total intracellular concentrations for intracellular drug activity, in particular drug metabolism, using isolated human hepatocytes and the integrated cell models.

Finally, in collaboration with the University of California San Francisco, drug interactions with the renal transporters OAT1 and OAT3 and with the extraneuronal monoamine transporter OCT3 have been studied for more than two thousand drugs and drug-like compounds. Computational structure-activity relationship analyses have been finalized, revealing molecular properties that influence the risk for drug-transporter interactions, and that affect the specificity towards certain transporter isoforms. Manuscripts are currently under preparation.

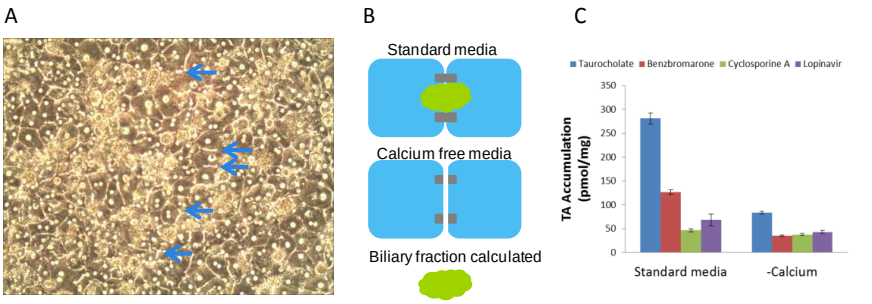

Fig 1. During 2012, a new in vitro model based on highly differentiated human hepatocytes was established. The model is used for studies of biliary drug clearance and drug induced liver injury, e.g. mediated by intracellular accumulation of bile acids. A) Sandwich cultured human hepatocytes at day 5 of culture. Biliary networks have formed and are indicated by the blue arrows. B) Experiments are run in parallel in standard media that maintain the integrity of tight junctions and bile canaliculi and in calcium free media that interrupt the tight junctions and open the bile canaliculi. This allows determination of the amount of drug accumulated in the biliary network and determination of bile clearance. C) Taurocholate accumulation in control incubations and in presence of transport inhibitors

In the biopharmaceutical field our research on optimizing and rationalizing formulation of poorly soluble compounds was continued during 2012 to now include well established collaboration within the department and with external partners (Monash University, University of California Irvine, Medicinal Products Agency in Sweden and big pharma). The primary goal is to develop in silico models that predict formulation strategies for poorly soluble compounds from molecular structure alone. For this purpose, solid-state transformations focusing on amorphous material have been analyzed in depth and structural features promoting glass-forming ability and dry stability of amorphous material have been identified. Late 2012 the first paper in which computational predictions of drug loading capacity of excipients commonly used in lipid-based formulations was submitted. In addition to the formulation directed work, research on intestinal solubility and risk of food effects continued and a major study on how ethanol may increase the solubility and dissolution rate was published. Current projects are directed towards prediction of supersaturation and precipitation in intestinal fluids, and in silico modeling of apparent solubility in the fasted and fed state. Parts of this research will be performed in the European collaboration OrBiTo, which is an IMI-funded project. In addition, the research within solid state transformation will continue during 2013, and the pharmaceutical cocrystal approach will likely be covered in new established collaboration with University of Copenhagen. The lipid-based formulations will be further explored, as will microstructures and lipid aggregates formed in intestinal fluids. The latter will be investigated with Molecular Dynamics Simulations together with Lancaster University.

Last, but not least, our collaborative platform for pharmaceutical profiling (physicochemical, ADMET and preclinical formulation) experienced a healthy growth in both staff and activities during 2012. However, the demand for UDOPP participation in Swedish drug discovery and development projects remains much larger than what UDOPP can supply. Over the last two years, the number of projects at UDOPP has increased with 200 % and during the last year, a total of 32 small and large projects were active at UDOPP, divided between 8 large projects (> 4 weeks of 1 FTE), 13 smaller projects (1-4 weeks of 1 FTE), 6 open access projects and 3 larger and 2 smaller

development projects. As an example of the latter, UDOPP has, in collaboration with the Broad Institute of Harvard and MIT been granted a post doc position from AstraZeneca and initiated studies aiming to explore and develop a rule system for ADME properties beyond the traditional drug-like chemical space. The first proof-of-principle study is near completion and will be communicated during 2013. Fig. 2 shows the wide range of ADMET methodologies available at UDOPP.

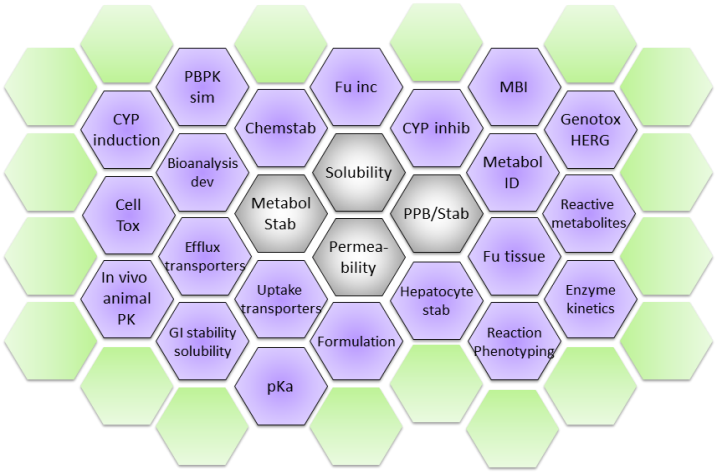

Fig 2. UDOPP in vitro assays. The chemical and metabolic stability, solubility, plasma protein binding and permeability studies determine fundamental properties of new chemical entities (NCE) that influences many processes in drug delivery such as absorption, distribution, metabolism and elimination (ADME). This information is crucial for adequate planning and interpretation of the efficacy studies and therefore, this type of studies are core experiments which are performed routinely for NCEs (grey colored assays). As the NCEs show expected effect in efficacy studies and are progressing in drug discovery and development process, more specific ADME and in vitro drug-drug interactions studies are need e.g. in order to investigate which kind of metabolic enzymes and drug transporters are involved in clearance of the NCEs and for early identification possible risk(s) for clinical significant drug-drug interactions, respectively (pink colored assays). Some additional assays for early determination of toxicity, i.e. HERG assay and in vivo animal PK studies are performed in collaboration with UDOPP external partners.

Members of the group during 2012

Per Artursson, Professor

Ulf Norinder, Adjunct professor

Christel Bergström, Associate professor

Sara Andersson, MPharm

Maria Backlund, Research scientist

Pawel Baranczewski, Research scientist

Jonas Fagerberg, PhD Student

Jenny Felth, Research scientist

Luca Fenu, Research scientist

Maria Karlgren, Research scientist

Patrik Lundquist, Research scientist

Maria Mastej, BSc

André Mateus, PhD Student

Pär Matsson, Research scientist

Christian Pedersen, PhD Student

Jenny Pedersen, PhD Student

Linda Persson, PhD Student

Linda Strandenhed

Elin Svedberg, MPharm

Richard Svensson, Research scientist

Anna Vildhede, PhD Student

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1. Ahlin, G, Chen, L, Lazorova, L, Chen, Y, Ianculescu, A, Davis, RL, Giacomini, KM and Artursson, P. Genotype Dependent Effects of Inhibitors of the Organic Cation Transporter, OCT1: Predictions of metformin interactions. *The Pharmacogenomics Journal*, 2011, 11 (6), 400.
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6. Schlessinger, A, Matsson, P, Shima, JE, Pieper, U, Yee, SW, Kelly, L, Apeltsin, L, Stroud, RM, Ferrin, TE, Giacomini, KM and Sali, A. Comparison of human solute carriers. *Protein Science*, 2010, 19 (3), 412.
7. Sugano, K, Kansy, M, Artursson, P, Avdeef, A, Bendels, S, Di, L, Ecker, GF, Faller, B, Fischer, H, Gerebtzoff, G, Lennernäs, H and Senner, F.. In vitro ADMET and physicochemical investigations of poly-N-methylated peptides designed to inhibit Abeta aggregation. *Nature Reviews in Drug Discovery*, 2010, 9 (8), 597.
8. Unga, J, Matsson, P and Mahlin, D. Understanding polymer-lipid solid dispersions-The properties of incorporated lipids govern the crystallisation behaviour of PEG. *International Journal of Pharmaceutics*, 2010, 386 (1-2), 61.
9. Zaki, NM, Artursson, P and Bergström, CAS. A Modified Physiological BCS for Prediction of Intestinal Absorption in Drug Discovery. *Molecular Pharmaceutics*, 2010, 7 (5), 1478.
10. Rodriguez-Antona, C, Gomez, A, Karlgren, M, Sim, SC and Ingelman-Sundberg, M. Molecular genetics and epigenetics of the cytochrome P450 gene family and its relevance for cancer risk and treatment. *Human Genetics*, 2010, 127 (1), 1.

Funding

The group (including UDOPP) receives funding from the Swedish Research Council (infrastructure, medical and science branches), Swedish Governmental Agency for Innovation Systems, European Commission (innovative medicines initiative and large collaborative project), The Medical Products Agency, SciLifeLab (Uppsala and Stockholm), National Institutes of Health, Nordforsk, OE and Edla Johanssons Scientific Foundation and Industry.

Arrangement of research seminars and courses 2012

1. Research seminar; Intestinal Uptake Transporters for Oral Delivery, March 12, 2012. Prof Ikumi Tamai, Department of Membrane Transport and Biopharmaceutics, Faculty of Pharmacy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University.
2. Short Course; Human *in vitro* Systems for Predicting Drug Transport, Metabolism and Adverse Effects. 19th MDO Meeting and 12th European ISSX Meeting. June 17-21 2012. Noordwijk aan Zee, The Netherlands.
3. Symposium; 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Uppsala, September 26, 2012.
4. PhD course; Cell culture methodologies, September 3-7, 2012. Department of Pharmacy, Uppsala University.

Presentations at symposia and congresses 2012

Abstracts Posters

1. Srinivas Kitambi, S, Niklasson, M, Day, K, Matsson, P, Svensson, R, Usoskin, D, Sekyrova, P, Abdelhady, S, Toledo, EM, Nyah Tekeoh, G, Gyllborg, D, Arenas, E, Artursson, P, Andang, M, Hovatta, O, Hammarström, L and Ernfors, P. High Content Screen Identifies Modulators Selectively Increasing Embryonic Stem Cell Proliferation or Inhibiting Cancer Stem Cell Survival. Gordon research conference. February 26 - March 2, 2012. Texas, USA.
2. Almqvist, F, Artursson, P, Axelsson, H, Carlsson, M, Cullman, I, Elofsson, M, Enquist, P-A, Eriksson, J, Esberg, A, Gustavsson, A-L, Hammarström, L, Haraldsson, M, Jenmalm Jensen, A, Johansson, L, Lazorova, L, Lundbäck, T, Mastej, M, Qian, W, Sigmundsson, K, Svensson, R, Uvell, H, and Öhman, A. Chemical Biology Consortium Sweden, 3rd European Chemical Biology Symposium / 2nd Vienna Drug Action Conference. July 1-3, 2012. Vienna, Austria.
3. Karlgren, M, Vildhede, A, Wisniewski, JR, and Artursson, P. Classification of inhibitors of hepatic organic anion transporting polypeptides (OATPs) – influence of protein expression on drug-drug interactions. 2012 AAPS Annual Meeting and Exposition. October 14-18, 2012. Chicago, IL, USA.

4. Karlgren, M, Vildhede, A, Wisniewski, JR and Artursson, P. Variability in OATP Protein Expression and Influence on Atorvastatin uptake and drug-drug interactions. 2012 AAPS Annual Meeting and Exposition. October 14-18, 2012. Chicago, IL, USA.
5. Tehler, U, Fagerberg, JH, Svensson, R, Artursson, P and Bergström, CAS. A Prodrug rationale to transform a BCS Class 4 Compound to BCS Class 1. 2012 AAPS Annual Meeting and Exposition. October 14-18, 2012. Chicago, IL, USA.
6. Vildhede, A, Wisniewski, JR, Karlgren, M and Artursson, P. Global proteomic analysis of human liver – expression of proteins involved in ADMET processes. 2012 AAPS Annual Meeting and Exposition. October 14-18, 2012. Chicago, IL, USA.
7. Mateus, A, Matsson, P, Artursson, P. Impact of the Human OATP1B1 Transporter on Intracellular Unbound Drug Concentrations. 2012 AAPS Annual Meeting and Exposition. October 14-18, 2012. Chicago, IL, USA.
8. Vildhede, A, Wisniewski, JR, Karlgren, M, Norén, A and Artursson, P. Global proteomic analysis of human liver with focus on ADMET protein expression. 19th MDO Meeting and 12th European ISSX Meeting. June 17-21 2012. Noordwijk aan Zee, The Netherlands.
9. Karlgren, M, Vildhede, A, Norinder, U, Wisniewski, JR, Kimoto, E, Lai, Y, Haglund, U and Artursson, P. Classification of inhibitors of liver specific OATPS – influence of protein expression on drug-drug interactions. 19th MDO Meeting and 12th European ISSX Meeting. June 17-21 2012. Noordwijk aan Zee, The Netherlands.
10. Karlgren, M, Vildhede, A, Wisniewski, JR and Artursson, P. Variability in OATP Protein Expression and Influence on Atorvastatin uptake and drug-drug interactions. 19th MDO Meeting and 12th European ISSX Meeting. June 17-21 2012. Noordwijk aan Zee, The Netherlands.
11. Vildhede, A, Wisniewski, JR, Karlgren, M, Norén, A and Artursson, P. Global proteomic analysis of human liver with focus on ADMET protein expression. Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Uppsala, September 26, 2012.
12. Pedersen, C, Slepenkin, A, Peterson, E and Bergström, C. Gel formulation of poorly soluble drugs intended for prevention of HIV infection. Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Uppsala, September 26, 2012.
13. Persson, LC, Porter, CJ, Charman, N and Bergström CAS. Solubility of poorly soluble compounds in excipients of lipid based formulations. Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Uppsala, September 26, 2012.
14. Persson, LC, Porter, CJ, Charman, WN and Bergström, CAS. Solubility of poorly soluble compounds in excipients of lipid based formulations. Drug processing and delivery challenges and opportunities in controlled delivery and release. Södertälje, November 12-14, 2012.
15. Pedersen, JM, Hoogstraate, J, Bergström, CAS and Artursson, P. Investigation of Drug Interactions and Clinical Relevance with the Human Bile Salt Export Pump

(BSEP, ABCB11). Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Uppsala, September 26, 2012.

16. Pedersen, JM, Hoogstraate, J, Bergström, CAS and Artursson, P. Investigation of Drug Interactions and Clinical Relevance with the Human Bile Salt Export Pump (BSEP, ABCB11). Drug processing and delivery challenges and opportunities in controlled delivery and release. Södertälje, November 12-14, 2012.
17. Karlgren, M, Vildhede, A, Norinder, U, Wisniewski, JR, Kimoto, E, Lai, Y, Haglund, U and Artursson, P. Classification of inhibitors of hepatic organic anion transporting polypeptides (OATPs) – influence of protein expression on drug-drug interactions. 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Uppsala, September 26, 2012.
18. Karlgren, M, Vildhede, A, Wisniewski, JR and Artursson, P. Variability in OATP Protein Expression and Influence on Atorvastatin uptake and drug-drug interactions. 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Uppsala, September 26, 2012.
19. Bergström, CAS, Fagerberg, JH, Khalil, C and Mahlin, D. A Small-Scale Method to Measure Supersaturation Effects of Amorphous Compounds. AAPS Oct 14-18, 2012, Chicago, USA.
20. Bergström, CAS, Charman, WN and Porter, CJH. Forecasting druggability of targets from prospective computational assessment of biopharmaceutical performance of ligands. AAPS Oct 14-18, 2012, Chicago, USA.
21. Bergström, CAS, Charman, SA and Nicolazzo, JA. Computational prediction of CNS drug exposure based on a novel in vivo dataset, AAPS Oct 14-18, 2012, Chicago, USA.
22. Warren, D, Bergström, CAS, Anby, MU, Benameur, H, Porter, CJH and Pouton, CW. Structural determinants of polymeric precipitation inhibitors for use with poorly water soluble drugs. AAPS Oct 14-18, 2012, Chicago, USA.
23. Mahlin, D and Bergström, CAS. Early drug development predictions of glass formation and stability. AAPS Oct 14-18, 2012, Chicago, USA.
24. Tehler, U, Fagerberg, JH, Svensson, R, Artursson, P and Bergström, CAS. A Prodrug Rationale to Transform a BCS Class 4 Compound to BCS Class 1 AAPS Oct 14-18, 2012, Chicago, USA.
25. Köck, K, Ferslew, B, Netterberg, I, Yang, K, Urban, TJ, Stewart, P and Brouwer, KLR. Inhibition of the hepatic basolateral bile acid transporter MRP4 predicts cholestatic drug-induced liver injury (DILI), Poster by UU student, Ida Netterberg, the American Association for the Study of Liver Diseases in Boston.
26. Matsson, P, Kido, Y and Giacomini, KM. Profiling of a Prescription Drug Library for Potential Renal Drug-Drug Interactions Mediated by the Organic Cation Transporter 2. Symposium on Pharmaceutical Profiling in Drug Discovery and Development. Uppsala, September 26, 2012.

Abstracts Oral Presentation

1. Artursson, P. Impact of pharmaceutical profiling in Swedish academic drug discovery programs. 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. September 26th, 2012. Uppsala, Sweden.
2. Matsson, P. Exploring the human drug transporter interactome. 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. September 26th, 2012. Uppsala, Sweden.
3. Bergström, CAS. Formulate-ability - a crucial molecular property in drug development. 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. September 26th, 2012. Uppsala, Sweden.
4. Karlgren, M. Cell models for studying OATP-mediated drug transport. 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. September 26th, 2012. Uppsala, Sweden.
5. Fenu, L. Predicting the impact of transporters on oral drug absorption. 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. September 26th, 2012. Uppsala, Sweden.
6. Vildhede, A. Proteomics of hepatic membrane transporters. 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. September 26th, 2012. Uppsala, Sweden.
7. Mateus, A. Models for assessing intracellular drug exposure. 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development. September 26th, 2012. Uppsala, Sweden.
8. Fagerberg, JH. Physiologically based solubility and dissolution profiling of poorly soluble drugs. Nordforsk Meeting. February 8th, 2012. Helsinki, Finland.
9. Artursson, P. Pharmaceutical Profiling at UDOPP – assays and SAR in ADMET. Lunch seminar series at Uminova Science Park. February 8, 2012. Umeå, Sweden.
10. Fagerberg, JH. Ethanol effects on apparent solubility of poorly soluble drugs in simulated intestinal fluid. CRS Nordic Chapter meeting: Drug Delivery and Targeting. June 4th, 2012, Reykjavik, Iceland.
11. Artursson, P. Prediction of drug absorption today and tomorrow. EDAN meeting. March 25-27, 2012. Leuven, Belgium.
12. Arturson, P. Uppsala University Drug Optimization and Pharmaceutical Profiling Platform (UDOPP) A Node in CBCS. Nordic Chemical Biology Meeting, Uppsala, Sweden. May 2, 2012.
13. Artursson, P. 2D cell culture and subcellular models from intestine and liver for studies of drug transport, drug-drug transporter interactions and transporter-mediated side effects. 19th MDO Meeting and 12th European ISSX Meeting. June 17-21 2012. Noordwijk aan Zee, The Netherlands.
14. Pedersen, JM. Investigation of Drug Interactions and Clinical Relevance with the Human Bile Salt Export Pump (BSEP, ABCB11). Drug processing and delivery challenges and opportunities in controlled delivery and release. Södertälje, November 12-14, 2012.

15. Svensson, R. ADMET Profiling in Drug Discovery. Graduate HTS-course, Umeå University. 2012-03-19. Umeå, Sweden.
16. Mateus, A, Matsson, P and Artursson, P. A new method for determination of intracellular unbound drug concentrations in simple cell cultures: Impact of active uptake via OATP1B1. 2012 GPEN Meeting. November 28-December 2, 2012. Melbourne, Australia.
17. Karlgren, M. Transporters important for drug distribution - polymorphic aspects. SafeSciMET course, August 28 2012. Karolinska Institutet, Stockholm, Sweden.
18. Bergström, CAS. Department of Pharmacy Day Can a 'late' international qualification period make a difference? And to who? Oct 9, 2012, Uppsala Sweden.
19. Bergström, CAS. Drug Delivery Australia Meeting 2012. Formulate-ability: a crucial molecular property in drug development. Nov 27, 2012, Melbourne, Australia.
20. Artursson, P. Prediction and modeling of drug transport, drug-drug interactions and transporter mediated side effects. Drug processing and delivery. Challenges and opportunities in controlled delivery and release. Södertälje, November 12-14, 2012.
21. Artursson, P. Permeability/Transporters. 2012 GPEN Meeting. November 28-December 2, 2012. Melbourne, Australia.
22. Artursson, P. Prediction and modeling of drug transport, drug-drug interactions and transporter-mediated side effects. Almirall, Barcelona, Spain. January 27, 2012.
23. Karlgren, M. In vitro models for prediction of drug transport and drug metabolism. Faculty of Pharmacy day, Sept 20, 2012, Uppsala. Sweden.
24. Karlgren, M. The Uppsala Univerisity Optimization and Profiling Platform (UDOPP). Astra Zeneca, June, 2012. Mölndal, Sweden.
25. Fenu, L. Structure-based tools in early drug discovery – for quantification of active and passive transport processes. Roche Postdoctoral Symposium, 19-20 Nov, 2012, Penzberg, Germany.

Pharmacy Practice and Policy

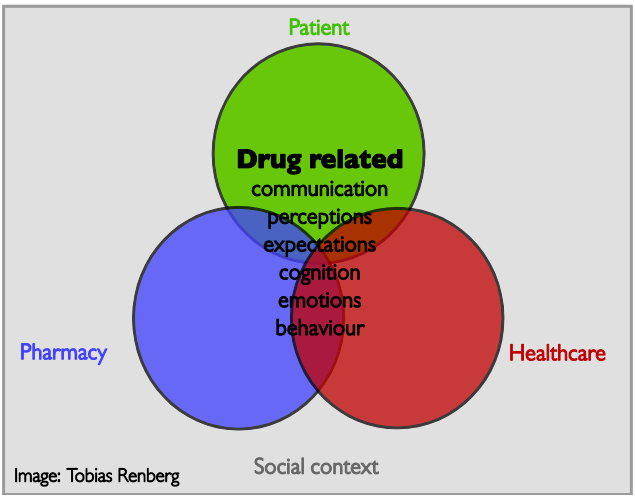
Senior Lecturer Sofia Kälvemark Sporrong

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.

We also conduct research on quality of life, the individual's subjective experience of his/her functioning and well-being. For example, we assess whether monitoring cancer patients with individualized quality of life instruments in clinical practice might improve patient outcomes. Another research interest is that of how patients view research (including being part of research projects) and researchers.



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

Åsa Kettis Lindblad, 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.

The pharmacy professions

Sofia Kälvemark Sporrong, Erika Olsson, Tobias Renberg, Jenny Rubensdotter Carlsson

The role of pharmacists is changing in Sweden due to new prerequisites on the pharmacy market. The public debate on pharmacists and their role has been studied through print media. Also, pharmacists and their work in pharmacies are studied, e.g. their view on generic substitution.

Patient reported outcomes

Hanna Fagerlind, Mathilde Hedlund Lindberg, Åsa Kettis Lindblad, Lena Ring

In evaluating interventions aiming at improving care and treatment, we pay attention to patient reported outcomes (PROs), e.g. patient satisfaction and quality of life (QoL). We explore the potential usefulness of incorporating PROs as tools in clinical practice, to make treatment and care more patient-centred, by using individualized quality of life assessments to monitor care and treatment of GI-cancer patients.

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 2012

Sofia Kälvemark Sporrong, Senior lecturer

Ida Bergström, Lecturer

Hanna Fagerlind, PhD Student

Pia Frisk, PhD Student

Mathilde Hedlund Lindberg, Research scientist

Malin Masterton, Research scientist

Erika Olsson, Research assistant

Jannike Stenlund, Lecturer

Kristin Wisell, PhD Student

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.
8. Siponen, SM, Ahonen, RS, Kettis, Å and Hameen-Anttila, KP. Complementary or alternative?: Patterns of complementary and alternative medicine (CAM) use among Finnish children. *European Journal of Clinical Pharmacology*, 2012, 68 (12), 1639.

Publications, reviews and book chapters 2011

1. Fagerlind, H, Bergström, I, Kettis Lindblad, Å, Velikova, G, Glimelius, B, and Ring, L. Communication analysis in oncology care: Performance of a combination of a content analysis system and a global scale. *Psycho-Oncology*, 2011, 20 (9), 992.
2. Hoefer, S, Pfaffenberger, N, Renn, D, Platter, M and Ring, L. Coronary Intervention Improves Disease Specific Health-Related Quality of Life but Not Individualised Quality of Life: A Potential Response Shift Effect? *Applied Research in Quality of Life*, 2011, 6 (1), 81.
3. Patrick, DL, Burke, LB, Gwaltney, CJ, Leidy, NK, Martin, ML, Molsen, E and Ring, L. Content Validity - Establishing and Reporting the Evidence in Newly Developed Patient-Reported Outcomes (PRO) Instruments for Medical Product Evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 1 - Eliciting Concepts for a New PRO Instrument. *Value in Health*, 2011, 14 (8), 967.

4. Patrick, DL, Burke, LB, Gwaltney, CJ, Leidy, NK, Martin, ML, Molsen, E and Ring, L. Content Validity - Establishing and Reporting the Evidence in Newly Developed Patient-Reported Outcomes (PRO) Instruments for Medical Product Evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 2 - Assessing Respondent Understanding. *Value in Health*, 2011, 14 (8), 978.
5. Renberg, T, Wichman Törnqvist, K, Kälvemark Sporrong, S, Kettis Lindblad, Å, Tully, MP. Pharmacy users' expectations of pharmacy encounters: a Q-methodological study. *Health Expectations*, 2011, 14 (4), 361.
6. Tully, MP, Beckman-Gyllenstrand, A and Bernsten, CB. Factors predicting poor counselling about prescription medicines in Swedish community pharmacies. *Patient Education and Counseling*, 2011, 83 (1), 3.
7. Wallman, A, Gustavsson, M, Kettis Lindblad, Å and Ring, L. An Exploration of How Students Learn in a Pharmacy Internship. *Pharmacy Education*, 2011, 11 (1), 177.
8. Wallman, A, Kälvemark Sporrong, S, Gustavsson, M, Kettis Lindblad, Å, Johansson, M and Ring, L. Swedish Students' and Preceptors' Perceptions of What Students Learn in a Six-Month Advanced Pharmacy Practice Experience. *American Journal of Pharmaceutical Education*, 2011, 75 (10), 197.
9. Wettergren, L, Kettis Lindblad, Å, Glimelius, B and Ring, L. Comparing two versions of the Schedule for Evaluation of Individual Quality of Life in patients with advanced cancer. *Acta Oncologica*, 2011, 50 (5), 648.

Publications, reviews and book chapters 2010

1. Fagerlind, H, Ring, L, Brülde, B, Feltelius, N and Lindblad, ÅK. Patients' understanding of the concepts of health and quality of life. *Patient Education and Counseling*, 2010, 78 (1), 104.
2. Ljungberg, C, Schwan, A, Morlin, C, Lindblad, ÅK and Tully, MP. Doctors' perspectives of responsibility for patient's drugs. *Pharmacy World & Science*, 2010, 32 (5), 689.
3. McGee, H and Ring, L. Quality of life in *Blackwell Health Psychology* 2nd edition. Eds French, Vedhara, Kaptein, Weinman for Wiley Blackwell, 2010.
4. Moen, J, Antonov, K, Nilsson, J.LG and Ring, L. Interaction Between Participants in Focus Groups With Older Patients and General Practitioners. *Qualitative Health Research*, 2010, 20 (5), 607.
5. Moen, J, Norrgård, S, Antonov, K, Nilsson, J.LG and Ring, L. GPs' perceptions of multiple-medicine use in older patients. *Journal of Evaluation In Clinical Practice*, 2010, 16 (1), 69.
6. Montgomery, A, Kälvemark Sporrong, S, Manap, N, Tully, MP and Kettis Lindblad, Å. Receiving a pharmaceutical care service compared to receiving standard pharmacy service: How do patients in Sweden differ with regard to perceptions of medicine use and the pharmacy encounter? *Research in Social and Administrative Pharmacy*, 2010, 6 (3), 185.

7. Montgomery, AT, Lindblad, ÅK, Eddby, P, Söderlund, E, Tully, MP and Kälvemark Sporrong, S. Counselling behaviour and content in a pharmaceutical care service in Swedish community pharmacies. *Pharmacy World & Science*, 2010, 32 (4), 455.
8. Nordén-Hägg, A, Andersson, K, Kälvemark Sporrong, S, Ring, L and Kettis Lindblad, Å. Reducing dispensing errors in Swedish pharmacies: the impact of a barrier in the computer system. *Quality and Safety in Healthcare*, 2010, 19 (6), e22.
9. Nordén-Hägg, A, Sexton, JB, Kälvemark Sporrong, S, Ring, L and Kettis Lindblad, Å. Assessing safety culture in pharmacies: the psychometric validation of the Safety Attitudes Questionnaire (SAQ) in a national sample of community pharmacies in Sweden. *BMC clinical pharmacology*, 2010, 10, 8.
10. Ring, L, Gross, C and McCall, E. Putting the text back into context: toward increased use of mixed methods for quality of life research. *Quality of Life Research*, 2010, 19 (5), 613.
11. Ylinen, S, Hameen-Anttila, K, Sepponen, K, Kettis Lindblad, Å and Ahonen, R. The use of prescription medicines and self-medication among children: a population-based study in Finland. *Pharmacoepidemiology and Drug Safety*, 2010, 19 (10), 1000.

Doctoral dissertation

Fagerlind, H. Patient-physician communication in oncology care: The character of, barriers against, and ways to evaluate patient-physician communication, with focus on the psychosocial dimensions. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 167, 2012.

Presentations at symposia and congresses 2012

1. Kälvemark Sporrong, S. Oral presentation. Hur kan jag få mina patienter att ta sina läkemedel på rätt sätt. ST-läkardagarna. January 26, 2012. Stockholm, Sweden.
2. Kälvemark Sporrong, S. Oral presentation. Etik i vårdarbete. Svenska ortodonti-föreningens årsmöte. March 16, 2012. Gothenburg, Sweden.
3. Kälvemark Sporrong, S & Carlsson Rubensdotter J. Den osynliga apotekaren. Apoteksmarknadsdagarna. March 22, 2012. Stockholm, Sweden.
4. Wisell, K. Oral presentation. The role of the pharmacies in health care; this way pharmacists could benefit society most. Almedalen. July 4, 2012. Visby, Sweden.
5. Fagerlind, H. Poster presentation. Oncologists' perceptions of psychosocial communication during outpatient visits – barriers and orientation. International Society for Quality of Life, 19th Annual conference. October 24-27, 2012. Budapest, Hungary.

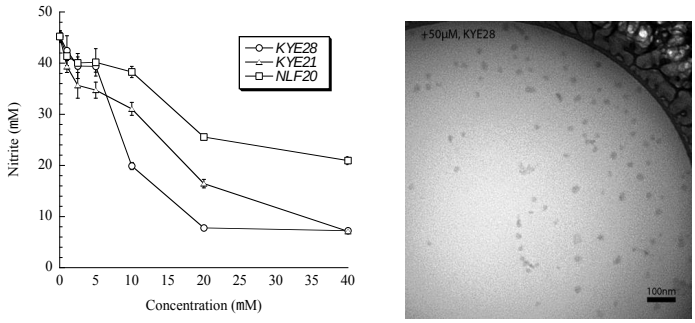
6. Olsson, E. Oral presentation. Generiskt utbyte med patienten i fokus. Om kommunikation kring generiskt utbyte med den känslige patienten. Läkemedelskongressen. November 6, 2012. Stockholm, Sweden.

7. Kälvemark Sporrong, S. Oral presentation. Etik. Läkemedelskongressen. November 6, 2012. Stockholm, Sweden.

Pharmaceutical Physical Chemistry

Professor Martin Malmsten

The development of modern pharmaceuticals places increasing emphasis on safe and efficient drug delivery. For example, many new synthetic pharmaceuticals are sparingly soluble in aqueous solution, and different types of colloidal drug carrier systems are required to solubilize the active components. Simultaneously, the importance of biotechnological drugs, notably proteins and peptides, has increased during the last decades. While generally water-soluble, these are frequently easily degradable both chemically and enzymatically, and may also loose their biological activity through conformational changes and aggregation. In order to maintain their biological activity, and in order to better control their interaction with the biological system (e.g., immune responses, circulation times, and uptake), they must frequently be administered together with drug carriers of a qualitatively similar type as those used for sparingly soluble synthetic drugs. Given this, we are therefore focusing on these aspects in our research. In doing so, we currently devote particular attention to antimicrobial and host-defense peptides, which offer potential as novel antibiotics and immune-modulating drugs, respectively.



(Left) Effects of the heparin cofactor II-derived peptides on NO production by macrophages. (Right) Peptide anti-endotoxic properties of these are correlated to their ability to fragment and compact LPS aggregates.

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). From this, we have been able to demonstrate a clear correlation between lipid membrane defect formation and peptide adsorption density, and how this can be controlled by peptide properties. A detailed analysis on the mechanism of action of these peptides has been facilitated by application of state-of-the-art experimental methodologies, involving collaboration with methodology experts (e.g., high resolution AFM, advanced electrochemical methodologies, solid state NMR, dual polarization interferometry, and Langmuir monolayer measurements), indicating that the pinning of peptide positive charges in the polar headgroup region of the lipid membranes causes localized packing defects. Recently, we have extended this work to investigations of the interaction between such peptides with lipopolysaccharide, both in solution and at bacterial as well as eukaryotic cell membranes, and consequences thereof on inflammation. 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.

Project area 2: Interaction between microgels and proteins/peptides

Prof Martin Malmsten, Prof Per Hansson, Ronja Månsson, 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. This research also addresses the role of excess electrolyte and pH on peptide loading/release, peptide distribution and transport kinetics within the gels, and degree of gel swelling/deswelling, and is based on a method combination of micromanipulator-assisted light microscopy, confocal microscopy, circular dichroism, and fluorescence spectroscopy. Recently, we extended this work to include studies of biodegradable microgels, of microfluidics-based microgel generation, and of factors determining protection from proteolytic degradation for microgel-loaded peptides. Within this research area, we are also investigating microgel interactions with physicochemically well-defined proteins, regarding effect of protein-polymer charge contrast and the degree of electrostatic screening.

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 temperature-sensitive poly(N-isopropyl acrylamide) core/poly(N-isopropyl methacrylamide). The results highlight the importance of the elastic coupling between phases coexisting in microgels. We have also successfully modeled the interaction between charged spherical polymer networks and oppositely charged proteins, peptides and surfactant micelles. The results explain 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. The project is funded by the Swedish Research Council.

Project area 5: Surface activity of lipoproteins in atherosclerosis

Prof Martin Malmsten, Prof Günter Siegel

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

Members of the group during 2012

Martin Malmsten, Professor

Per Hansson, Professor

Anders Ericsson, Associate professor

Eloi Feitosa, Visiting professor

Günter Siegel, Visiting professor

Jonas Gernandt, PhD Student

Claes Jidheden, PhD Student

Ronja Månsson, PhD Student

Shalini Singh, PhD Student

Lise-Britt Wahlberg, Technician

Publications, reviews and book chapters 2012

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Funding

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

Presentations at symposia and congresses 2012

1. Malmsten, M. Peptides and proteins in polyelectrolyte microgels. 26th Conference of the European Colloid and Interface Society, Malmö, September 5, 2012. Invited lecture.
2. Hansson, P. Segregation and mixing of proteins in polyelectrolyte gels. 26th Conference of the European Colloid and Interface Society, Malmö, September 5, 2012. Poster presentation.
3. Gernandt, J. Phase phenomena in hydrogel materials. Chalmers annual materials conference & Swedish chemical society, Division of surface chemistry and materials chemistry annual symposium: Materials for tomorrow. October 25, 2012. Invited talk.

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 translational research, i.e. 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, currently focused on topical drug delivery systems (gels).

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 2012

Project groups	*Projects*
Amorphous solids	(a) Properties of amorphous composites (b) Prediction of disordering propensity of solids
Process modelling	(a) Modelling of powder flow (b) Modelling of powder compression/compaction
Particle technology	(a) Formulation tools for characterizing particle mechanics and powder compactibility (b) Multiscale structure-property relationships for granular solids (c) Mechanical amorphization of particles
Controlled release	(a) Formulations for mucosal and transdermal drug delivery

Project area 1: Amorphous solids

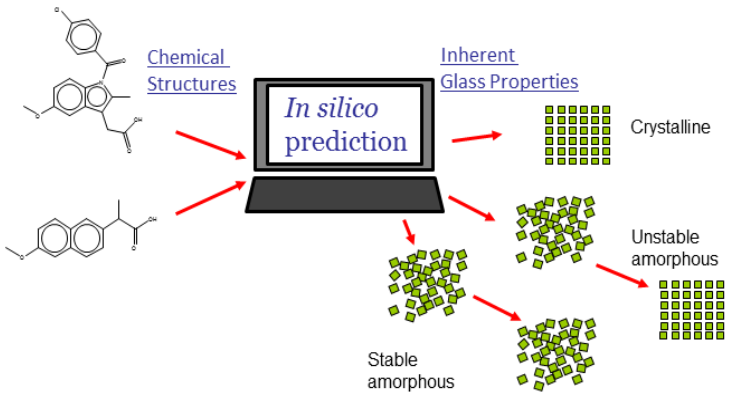
Principle investigator: Denny Mahlin

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 2012, 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. 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 alterations 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 over all aim is to better understand the fundamental properties that govern the ability of a solid material to become a stable amorphous solid, both during storage and dissolution.

Project area 2: Process modelling

Principle investigator: Göran Frenning

Powder technology is expected to underlie many of the manufacturing processes used in the pharmaceutical sector in the foreseeable future, especially for the ubiquitous solid oral dosage forms (tablets, capsules, etc.). A typical powder comprises a very large number of particles, implying that powder processes are inherently demanding to model on the particle scale. Such models nevertheless have a decisive value for understanding and prediction of the relationship between particle and powder properties. Our work is therefore directed towards the development and experimental evaluation of particle-scale models for common unit operations.

During 2012, the following projects have been running within the group:

(a) Modelling of powder flow

Powder flow is generally characterised by limited particle deformation, implying that relatively simple models that assume independent contacts are realistic. Current work in our group is directed towards experimental evaluation of discrete element models, focusing on shearing and effects of rolling friction.

(b) Modelling of powder compression/compaction

Powder compression/compaction is generally characterised by significant particle deformation and/or fracture. The current focus of our work is the development of simplified models for the behaviour of individual particles under confined conditions that can be utilised in discrete element simulations. Procedures to enforce the constraint imposed by plastic incompressibility are investigated.

Project area 3: Particle technology

Principle investigator: Göran Alderborn

Regardless of route of administration, powder science knowledge is critical in the development of solid dosage forms and solid dosage form technology has been an important research direction of the group for more than 20 years. Based on our knowledge on the compression and compaction of powders, we will continue to investigate the use of simple models as a means to derive measures of and predict particle properties. More on, we will continue our ambition to develop a theoretical framework for the properties of granular solids with a special reference to powder compaction.

During 2012, 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 macro-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 amorphization 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 amorphize the particles, causing alterations in the chemical and physical properties of the solid. We intend to investigate the amorphization of particles during powder flow and the type of inter-particulate contact processes that may cause amorphization. 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: Controlled release

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 2012, 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 2012

Göran Alderborn, Professor

Erik Björk, Senior lecturer

Ragnar Ek, Associate professor

Göran Frenning, Associate professor

Johan Gråsjö, Engineerer

Christin Magnusson, Lecturer

Denny Mahlin, Assistant professor

Lucia Lazorova, PhD

Josefina Nordström, Research scientist

Mina Heidarian, PhD Student

Joel Hellrup, PhD Student

Foad Mahmoodi, PhD Student

Samaneh Pazesh, PhD Student

Ann-Sofie Persson, PhD Student

Publications, reviews and book chapters 2012

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.

2. Mahmoodi, F, Alderborn, G and Frenning, G. An experimental evaluation of an effective medium based compaction equation. *European Journal of Pharmaceutical Sciences*, 2012, 46 (1-2), 49.
3. Nordstrom, J, Kievan, I and Alderborn, G. A protocol for the classification of powder compression characteristics. *European journal of pharmaceutics and biopharmaceutics*, 2012, 80 (1), 209.
4. Persson, A-S and Frenning, G. An experimental evaluation of the accuracy to simulate granule bed compression using the discrete element method. *Powder Technology*, 2012, 219, 249.
5. Salbu, L, Bauer-Brandl, A, Alderborn, G and Tho, I. Effect of degree of methoxylation and particle size on compression properties and compactibility of pectin powders. *Pharmaceutical development and technology*, 2012, 17 (3), 333.

Publications, reviews and book chapters 2011

1. Dew, N, Edsman, K and Björk, E. Novel Gel Formulations with Catanionic Aggregates Enable Prolonged Drug Release and Reduced Skin Permeation. *Journal of Pharmacy and Pharmacology*, 2011, 63 (10), 1265.
2. Dew, N, Edwards, K, Eriksson, J, Edsman, K and Björk, Erik. 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*, 2011, 89, 53.
3. Engmer Berglin, C, Videhult Pierre, P, Bramer, T, Edsman, K, Ehrsson, H, Eksborg, S and Laurell, G. Prevention of cisplatin-induced hearing loss by administration of a thiosulfate-containing gel to the middle ear in a guinea pig model. *Cancer Chemotherapy and Pharmacology*, 2011, 68 (6), 1547.
4. Frenning, G. Modelling drug release from inert matrix systems: From moving-boundary to continuous-field descriptions. *Internation Journal of Pharmaceutics*, 2011, 418 (1), 88.
5. Frenning, G, Gråsjö, J and Hansson, P. The Release of Catanionic Mixtures Embedded in Gels: An Approximate Analytical Analysis. *AIChE Journal*, 2011, 57 (6), 1402.
6. Gernandt, J, Frenning, G, Richtering, W and Hansson, P. A model describing the internal structure of core/shell hydrogels. *Soft Matter*, 2011, 7 (21), 10327.
7. Hellrup, J and Mahlin, D. Pharmaceutical micro-particles give amorphous sucrose higher physical stability. *Internation Journal of Pharmaceutics*, 2011, 409 (1-2), 96.
8. Jämstorp, E, Strømme, M and Frenning, G. Modeling structure-function relationships for diffusive drug transport in inert porous geopolymer matrices. *Journal of Pharmaceutical Sciences*, 2011, 100 (10), 4338.
9. Mahlin, D, Ponnambalam, S, Heidarian Höckerfelt, M, and Bergström, CAS. Toward In Silico Prediction of Glass-Forming Ability from Molecular Structure Alone: A Screening Tool in Early Drug Development. *Molecular Pharmaceutics*, 2011, 8 (2), 498.

10. Mahmoodi, F, Alderborn, G and Frenning, G. Effect of spherical-agglomerate strength on the distribution of force during uniaxial compression. *Powder Technology*, 2011, 206 (3), 283.

11. Nordström, J and Alderborn, G. Degree of compression as a potential process control tool of tablet tensile strength. *Pharmaceutical development and technology*, 2011, 16 (6), 599.

12. Persson, A-S, Alderborn, G and Frenning, G. Flowability of surface modified pharmaceutical granules: A comparative experimental and numerical study. *European Journal of Pharmaceutical Sciences*, 2011, 42 (3), 199.

13. Wessman, P, Mahlin, D, Akhtar, S, Rubino, S, Leifer, K, Kessler, V and Håkansson, S. Impact of matrix properties on survival of freeze-dried bacteria. *Journal of the Science of Food and Agriculture*, 2011, 91 (14), 2518.

14. Århammar, C, Pietzsch, A, Bock, N, Holmström, E, Araujo, CM, Gråsjö, J, Zhao, S, Green, S, Peery, T, Hennies, F, Amerioun, S, Foehlisch, A, Schlappa, J, Schmitt, T, Strocov, VN, Niklasson, GA, Wallace, DC, Rubensson, J-E, Johansson, B and Ahuja, R. Unveiling the complex electronic structure of amorphous metal oxides. *Proceedings of the National Academy of Sciences of the United States of America*, 2011, 108 (16), 6355.

Publications, reviews and book chapters 2010

1. Frenning, G. Compression mechanics of granule beds: A combined finite/discrete element study. *Chemical Engineering Science*, 2010, 65 (8), 2464.

2. Klevan, I, Nordström, J, Tho, I and Alderborn, G. A statistical approach to evaluate the potential use of compression parameters for classification of pharmaceutical powder materials. *European journal of pharmaceutics and biopharmaceutics*, 2010, 75 (3), 425.

3. Mahmoodi, F, Alderborn, G and Frenning, G. Effect of lubrication on the distribution of force between spherical agglomerates during compression. *Powder Technology*, 2010, 98 (1), 69.

4. Schoug, Å, Mahlin, D, Jonson, M and Håkansson, S. Differential effects of polymers PVP90 and Ficoll400 on storage stability and viability of Lactobacillus coryniformis Si3 freeze-dried in sucrose. *Journal of Applied Microbiology*, 2010, 108 (3), 1032.

5. Unga, J, Matsson, P and Mahlin, D. Understanding polymer-lipid solid dispersions-The properties of incorporated lipids govern the crystallisation behaviour of PEG. *International Journal of Pharmaceutics*, 2010, 386 (1-2), 61.

6. Wessman, P, Edwards, K and Mahlin, D. Structural effects caused by spray- and freeze-drying of liposomes and bilayer disks. *Journal of Pharmaceutical Sciences*, 2010, 99 (4), 2032.

Funding

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

Doctoral dissertation

Mahmoodi, F. Compression mechanics of powders and granular materials probed by force distributions and a micromechanically based compaction equation. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 159, 2012.

Presentations at symposia and congresses 2012

1. Hellrup, J. Stabilization of amorphous sugars with particles and the role of humidity. NordForsk Researcher Network Meeting, Helsinki, Finland, Febrary 7-8, 2012.
2. Hellrup, J. A stability study of composites consisting of amorphous lactose and nanoparticle additives. Drug Processing and Delivery, Södertälje, Sweden, November 12-14, 2012.
3. Mahlin, D. Amorphous drugs – finding the compounds that can retain solid state disorder during storage and dissolution, 4th Symposium on Pharmaceutical Profiling in Drug Discovery and Development, Uppsala, Sweden, September 26, 2012.
4. Mahmoodi, F. GaBi Award Lecture. Drug Processing and Delivery, Södertälje, Sweden, November 12-14, 2012.
5. Pazesh, S. The effect of compression and shearing on the activation (amorphisation) of micro-particles of griseofulvin. Drug Processing and Delivery, Södertälje, Sweden, November 12-14, 2012.

Abstracts Posters

1. Frenning, G. Towards a mechanistic model for the interaction between plastically deforming particles under confined conditions. AAPS annual meeting and exposition, Chicago, U.S., October 14-18, 2012.
2. Hellrup, J, Alderborn, G and Mahlin, D. Compressibility of spray-dried lactose and nanoparticle composites. Drug Processing and Delivery, Södertälje, Sweden, November 12-14, 2012.
3. Mahlin, D. and Bergström, CAS. Early Drug Development Predictions of Glass Formation and Stability, AAPS Annual Meeting, Chicago, USA, October 14-18, 2012.
4. Bergström, CAS, Fagerberg, JH, Khalil, C and Mahlin, D. A Small-Scale Method to Measure Supersaturation Effects of Amorphous Compounds. AAPS October 14-18, 2012, Chicago, USA.

5. Mahmoodi, F, Klevan, I, Nordström, J, Alderborn, G and Frenning, G. A comparison between two compression parameters representing indications of particle plasticity. AAPS annual meeting and exposition, Chicago, U.S., October 14-18, 2012.
6. Nordström, J, Persson, A-S, Lazorova, L, Frenning, G and Alderborn, G. The effect of degree of compression on the microstructure and tensile strength of tablets formed of granular solids. AAPS annual meeting and exposition, Chicago, U.S., October 14-18, 2012.
7. Nordström, J, Persson, A-S, Lazorova, L, Frenning, G and Alderborn, G. The effect of degree of compression on the microstructure and tensile strength of tablets formed of granular solids. Drug Processing and Delivery, Södertälje, Sweden, November 12-14, 2012.
8. Pazesh, S. The role of friction for the mechanical activation of solid griseofulvin. NordForsk Researcher Network Meeting, Helsinki, Finland, Febrary 7-8, 2012.
9. Pazesh, S. The effect of compression and shearing on the activation of micro-particles of griseofulvin, AAPS Annual Meeting, Chicago, USA, October 14-18, 2012.
10. Pazesh, S. The effect of compression and shearing on the activation of micro-particles of griseofulvin. Drug Processing and Delivery, Södertälje, Sweden, November 12-14, 2012.
11. Persson, A-S and Frenning, G. Shearing of non-cohesive granules: an experimental and numerical comparison. AAPS annual meeting and exposition, Chicago, U.S., October 14-18, 2012.
12. Persson, A-S and Frenning, G. Shearing of non-cohesive granules: an experimental and numerical comparison. Drug Processing and Delivery, Södertälje, Sweden, November 12-14, 2012.

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.

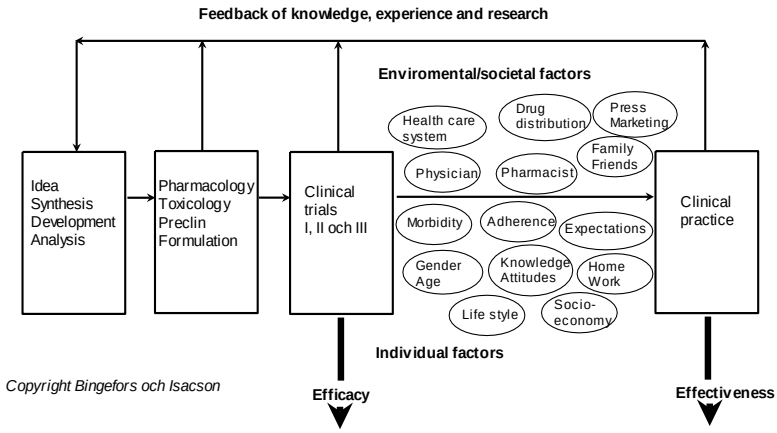


Figure 1. The development of drugs and efficacy/effectiveness of drug treatment

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. (In collaboration with the Centre for Gender Research)

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, drug treatment adherence and attitudes towards drugs

The importance of individual factors affecting the outcome of drug treatment is also an area of interest. A study of subjectively experienced adverse drug reactions and their association with self-perceived health status was concluded. The importance of

individual factors affecting the outcome of drug treatment is also an area of interest. A study of subjectively experienced adverse drug reactions and their association with self-perceived health status has been published. Currently, we are working with risk factors for decreased adherence to drug therapy in the population within a PhD project. In a first study non-adherence behaviors in and reasons for non-adherence have been analyzed from a gender perspective. In an ongoing study the importance of anxiety and depression is analyzed (Lena Thunander-Sundbom).

Members of the group during 2012

Dag Isacson, Professor

Kerstin Bingefors, Associate professor

Helena Wennborg, MD PhD

Lena Thunander Sundbom, PhD student

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.

Publications, reviews and book chapters 2011

1. Bingefors, K, Lindberg, M and Isacson, D. Quality of Life, Use of Topical Medications and Socio-economic Data in Hand Eczema: A Swedish Nationwide Survey. *Acta Dermato-Venereologica*, 2011, 91 (4), 452.

Publications, reviews and book chapters 2010

1. Edvinsson, D, Bingefors, K, Lindström, E and Lewander, T. ADHD-related symptoms among adults in out-patient psychiatry and female prison inmates as compared with the general population. *Uppsala Journal of Medical Sciences*, 2010, 115 (1), 30.
2. Koltowska-Häggström, M, Geffner, ME, Jönsson, P, Monson, JP, Abs, R, Hána, V, Höybye, C and Wollmann, HA. Discontinuation of Growth Hormone (GH) Treatment during the Transition Phase Is an Important Factor Determining the Phenotype of Young Adults with Nonidiopathic Childhood-Onset GH Deficiency. *Journal of Clinical Endocrinology and Metabolism*, 2010, 95 (6), 2646.
3. Lazurova, I, Pura, M, Wagnerova, H,Tajtakova, M, Sedlakova, M, Tomas, L, Payer, J, Hruzikova, P, Vanuga, P, Podoba, J, Trejbalova, L, Popovic, V and Koltowska-Häggström, M. Effect of Growth Hormone Replacement Therapy on

Plasma Brain Natriuretic Peptide Concentration, Cardiac Morphology and Function in Adults with Growth Hormone Deficiency. *Experimental and clinical endocrinology & diabetes*, 2010, 118 (3), 172.

Other information

Dissertations

1. Thörn, H. First-pass intestinal metabolism of drugs: Experiences from in vitro, in vivo and simulation studies. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 153, 2012.
2. Mahmoodi, F. Compression mechanics of powders and granular materials probed by force distributions and a micromechanically based compaction equation. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 159, 2012.
3. Carlert, S. Investigation and prediction of small intestinal precipitation of poorly soluble drugs: A study involving *in silico, in vitro* and *in vivo* assessment. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 164, 2012.
4. Fagerlind, H. Patient-physician communication in oncology care: The character of, barriers against, and ways to evaluate patient-physician communication, with focus on the psychosocial dimensions. Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 167, 2012.

Awards and appointments 2012

Malmsten, M. Nordblad-Ekstrand Medal, Swedish Chemical Society

Bergström, C. Adjunct Associate Professor, Monash University, Australia

Mahmoodi, F. Gabi Award, Swedish Academy of Pharmaceutical Sciences

Fellowships

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

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

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

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

Addresses

Department of Pharmacy
Uppsala University, BMC, Box 580, SE-751 23 Uppsala, Sweden
Tel +46 18 471 4472
Fax +46 18 471 4223
www.farmfak.uu.se/farm

Ahnfelt Emelie	emelie.ahnfelt@farmaci.uu.se
Alderborn Göran	goran.alderborn@farmaci.uu.se
Andersson Sara	sara.andersson@farmaci.uu.se
Artursson Per	per.artursson@farmaci.uu.se
Baranczewski Pawel	pawel.baranczewski@farmaci.uu.se
Bergström Christel	christel.bergstrom@farmaci.uu.se
Bergström Ida	ida.bergstrom@farmaci.uu.se
Backlund Maria	maria.backlund@farmaci.uu.se
Bingefors Kerstin	chris.bingefors@farmaci.uu.se
Björk Erik	erik.bjork@farmaci.uu.se
Dubbelboer Ilse	ilse.dubbelboer@farmaci.uu.se
Ek Ragnar	ragnar.ek@farmaci.uu.se
Ericsson Anders	anders.ericsson@farmaci.uu.se
Fagerberg Jonas	jonas.fagerberg@farmaci.uu.se
Fagerlind Hanna	hanna.fagerlind@farmaci.uu.se
Frenning Göran	goran.frenning@farmaci.uu.se
Gernandt Jonas	jonas.gernandt@farmaci.uu.se
Gråsjö Johan	johan.grasjo@farmaci.uu.se
Hansson Per	per.hansson@farmaci.uu.se
Hellrup Joel	joel.hellrup@farmaci.uu.se
Isacson Dag	dag.isacson@farmaci.uu.se
Jidheden Claes	claes.jidheden@farmaci.uu.se
Karlgren Maria	maria.karlgren@farmaci.uu.se
Kälvemark Sporrong Sofia	sofia.kalvemark-sporrong@farmaci.uu.se
Lazorova Lucia	lucia.lazorova@farmaci.uu.se
Lennernäs Hans	hans.lennernas@farmaci.uu.se

Lide Eva	eva.lide@farmaci.uu.se
Lilienberg Elsa	elsa.lilienberg@farmaci.uu.se
Lundquist Patrik	patrik.lundquist@farmaci.uu.se
Magnusson Christin	christin.magnusson@farmaci.uu.se
Mahlin Denny	denny.mahlin@farmaci.uu.se
Mahmoodi Foad	foad.mahmoodi@farmaci.uu.se
Malmsten Martin	martin.malmsten@farmaci.uu.se
Mastej Maria	maria.mastej@farmaci.uu.se
Mateus André	andre.mateus@farmaci.uu.se
Matsson Pär	par.matsson@farmaci.uu.se
Månsson Ronja	ronja.mansson@farmaci.uu.se
Nises Ahlgren Eva	eva.nises-ahlgren@farmaci.uu.se
Nordström Josefina	josefina.nordstrom@farmaci.uu.se
Ocklind Göran	goran.ocklind@farmaci.uu.se
Olsson Erika	erika.olsson@farmaci.uu.se
Pazesh Samaneh	samaneh.pazesh@farmaci.uu.se
Pedersen Christian	christian.pedersen@farmaci.uu.se
Pedersen Jenny	jenny.pedersen@farmaci.uu.se
Persson Ann-Sofie	ann-sofie.persson@farmaci.uu.se
Persson Linda	linda.persson@farmaci.uu.se
Rylén Birgitta	birgitta.rylen@farmaci.uu.se
Singh Shalini	shalini.singh@farmaci.uu.se
Sjögren Erik	erik.sjogren@farmaci.uu.se
Stenlund Jannike	jannike.stenlund@farmaci.uu.se
Strandenhed Linda	linda.strandenhed@farmaci.uu.se
Svedberg Elin	elin.svedberg@farmaci.uu.se
Svensson Richard	richard.svensson@farmaci.uu.se
Svensson Lindgren Annette	annette.svensson-lindgren@farmaci.uu.se
Thunander Sundbom Lena	lena.thunander-sundbom@farmaci.uu.se
Wahlberg Lise-Britt	lise-britt.wahlberg@farmaci.uu.se
Wennborg Helena	helena.wennborg@farmaci.uu.se
Vildhede Anna	anna.vildhede@farmaci.uu.se
Wisell Kristin	kristin.wisell@farmaci.uu.se
Wästberg Galik Ulla	ulla.wastberg-galik@farmaci.uu.se

Kph, Trycksaksbolaget AB, Uppsala 2013