Preface

Welcome to the Annual Report of the Department of Pharmacy at Uppsala University. Besides the chairman’s report, the report 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

[Signature]

Martin Malmsten
Chairman, Department of Pharmacy
# List of Contents

**Chairman’s report**  
- Research 7
- PhD education 7
- Undergraduate education 8
- Collaboration with society 9
- Personnel 9
- Administration and economy 9

**Organization and personnel** 11

**Scientific reports** 27
- Biopharmaceutics 29
- Drug Delivery 38
- Pharmacy Practice and Policy 49
- Pharmaceutical Physical Chemistry 56
- Pharmaceutics 65
- Pharmacoepidemiology and Pharmacoeconomics 74

**Other information** 79
- Dissertations 81
- Awards and Appointments 82
- Fellowships 83
- Address list 84
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)

<table>
<thead>
<tr>
<th>Description</th>
<th>Amount</th>
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</thead>
<tbody>
<tr>
<td>University funding - Undergraduate teaching</td>
<td>17,996</td>
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<td>Contract teaching</td>
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<td>University funding - Research and post-graduate teaching</td>
<td>22,522</td>
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<td>Research grants</td>
<td>8,936</td>
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<td>Commissioned research</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>52,557</strong></td>
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</tbody>
</table>
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, Assistant 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**

<table>
<thead>
<tr>
<th>PhD Students</th>
<th>Supervisors</th>
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<tbody>
<tr>
<td>Emelie Ahnfelt</td>
<td>Hans Lennernäs</td>
</tr>
<tr>
<td>Sara Carlert</td>
<td>Hans Lennernäs</td>
</tr>
</tbody>
</table>
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

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 Gräsjö, 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 pharmacoconomics. 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 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 Alumnforening, 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
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 treatments for liver cancer taking the role of local disposition in a diseased tissue into account. Building physiological based pharmacokinetic modelling with application to predicting and understanding the local disposition of drugs in liver cancer tissue and as well gastrointestinal drug absorption.

We are using advanced clinical research models (both in vivo and in vitro), which are well established in our laboratory (such GI-intubation techniques and Ussing chamber) to 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 as hydrocortisone replacement therapy in adrenal insufficiency. In addition, the biopharmaceutic research group is developing novel anti-cancer treatment approaches at various stages of development, providing exciting perspectives for the future of controlled release focal cancer cure. One important factor for a successful outcome of such therapeutic approaches is ensuring local specific targeting of the therapeutic moiety at the tumour site. In collaboration with clinical groups an increased understanding of the limitations of current therapies for liver cancer is the major objective. Based on this knowledge novel approaches for a more efficient and safe local chemotherapy is developed.

Professor Lennernäs is the inventor of more than 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 Veterinary 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 University hospital, and National Veterinary Institute
Figure 1. OrBiTo is a new European project within the IMI programme in the area of oral biopharmaceutics tool that includes 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


**Publications, reviews and book chapters 2011**


**Publications, reviews and book chapters 2010**


**Funding**

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

**Doctoral dissertations**


**Presentations at symposia and congresses 2012**


7. Lennernäs, H. Oral modified drug delivery: the importance of regional aspects on dissolution, permeability and metabolism, Pharmaceutical Profiling of Drugs, September 26, Uppsala.


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.


**Patents and patents applications**

15 patents and patents 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 interest. 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 devised 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.
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  
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Jenny Pedersen, PhD Student  
Linda Persson, PhD Student  
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Elin Svedberg, MPharm  
Richard Svensson, Research scientist  
Anna Vildhede, PhD Student

Publications, reviews and book chapters 2012


**Publications, reviews and book chapters 2011**


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.


4. PhD course; Cell culture methodologies, September 3-7, 2012. Department of Pharmacy, Uppsala University.

Presentations at symposia and congresses 2012

Abstracts Posters


15. Pedersen, JM, Hoogstrate, J, Bergström, CAS and Artursson, P. Investigation of Drug Interactions and Clinical Relevance with the Human Bile Salt Export Pump


Abstracts Oral Presentation


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


Publications, reviews and book chapters 2011


Publications, reviews and book chapters 2010


**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**


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 lose 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


59


Publications, reviews and book chapters 2011


Publications, reviews and book chapters 2010


**Funding**

The group receives funding from the Swedish Research Council and Industry.
Presentations at symposia and congresses 2012


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

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


**Publications, reviews and book chapters 2011**


Publications, reviews and book chapters 2010


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


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.


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, lifestyle, 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**


**Publications, reviews and book chapters 2011**


**Publications, reviews and book chapters 2010**

Dissertations


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.


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)
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