



APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER

ISSUE 2/2011

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DRUG DELIVERY EVENTS

Provided by Christoph Blümer

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Nail Forum

June 28, 2011, School of Pharmacy, University of London, UK

[Details](#)

38th Annual Meeting & Exposition of the Controlled Release Society

July 30 - August 3, 2011, National Harbor, MD, US (near Washington, DC)

[Details](#)

◇ Design and development of novel OTC products (APV course 6390)

November 7-8, 2011, Düsseldorf/Neuss, Germany

OTC-drug products comprise a significant portion of the total healthcare market and are of commercial interest for global, midsize and small drug companies. Brand name recognition and customer awareness are important goals in the marketing of these products. This is where line extensions and new dosage forms can serve as a valuable tool. Due to the fact that OTC products are based on well-known actives, innovative approaches in product development have to focus on other aspects compared to prescription products such as new dosages forms and new packaging devices. The technical term "innovation" has to be considered to a much larger extent from the perspective of the patient/customer and much less from a scientific point of view. This seminar presents a range of topics which are important in generating and realizing ideas for new products in the framework of OTC-marketing.

[Details](#)

[Suggest a meeting to be announced!](#)

APV COURSE SUMMARIES

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Parenteral Controlled Release Formulations (Written by Gerben Moolhuizen)

Berlin, Germany, November 23-24, 2010 and April 12-13, 2011

Presentations covering all aspects of the growing area of parenteral controlled release were given at the first APV "Parenteral Controlled Release Formulations" workshop which was held on November 23-24 2010 in Berlin. This course was organized by the APV focus group Drug Delivery for scientists working in different fields of drug product development such as formulation, drug delivery and preformulation. It was chaired by Prof Dr. Achim Goepferich (University of Regensburg, Germany) and Gerben Moolhuizen (OctoPlus, Leiden, The Netherlands). More than 35 people attended the course. The two-day schedule was divided into 17 sessions in which an international panel of experts balanced between industry, academia and regulators shared their knowledge with the audience.

Day 1

After a brief introductory presentation by Gerben Moolhuizen on the commercial role and prospects for parenteral controlled release, Dr. Barbara Lueckel of F. Hoffmann-La Roche started the day. She first gave an overview of the beginnings of the field and provided an up-to-date overview of the various approaches available to achieve long term release of injectable drugs. The course then explored two technologies that are the historical backbone of the field in more detail. First, Prof Dr. Goepferich gave the audience an historic perspective of the most widely used polymer in the field, poly(lactide-co-glycolide), as well as a very good overview of the pros and cons of this polymer. Next, Prof. Dr. Karsten Maeder, Halle University, presented an overview of the field of liposomal formulations, the other backbone technology for controlled release that has resulted in a number of successful products.

The program then moved to Prof Dr. Wim Hennink (Utrecht University, The Netherlands) who presented very interesting data on new polymers on the horizon. Dr. Karin Schoenhammer, Novartis, gave a presentation on in situ gelling. Dr. Christine Talling, (BayerSchering Pharma, Turku, Finland) focused her presentation on an area that have seen significant scientific and commercial success, namely non-biodegradable implantable systems. As the final speaker of Day 1, Prof. Dr. Robert Gurny (University of Geneva, Switzerland) engaged the audience with a talk on a field that hold a lot of promise and challenges: technologies for long term release of drugs in the eye. In his presentation, he covered recent, interesting work carried out by his group on a new injectable, biodegradable polymer for treatment of eye diseases. Day 1 ended with a panel discussion between speakers and attendees, which gave the audience a good opportunity to ask any questions they had.

Day 2

Day 2 of the program focused more on regulatory and development aspects, as well as on areas for future growth, such as long acting biopharmaceuticals. After introductory words from co-chair Prof. Dr. Goepferich, Dr. Ruud Verrijck (OctoPlus, The Netherlands) gave an inspiring presentation on getting a microsphere-product for the controlled release of interferon from the research bench to clinical proof-of-concept, giving insight into the practical issues to be overcome. He was followed by Dr. Sabine Hauck (Acino GmbH, Miesbach) who focused her presentation on the specific issues encountered when attempting to get regulatory approval for a generic injectable controlled release product. Her presentation was nicely complemented by the next, in which Dr. Katrin Buss from the German regulatory agency, BfArM, presented the regulatory requirements for depot formulations and biopharmaceuticals. The topic of biopharmaceuticals, and the specific challenges they pose in formulation development and drug delivery, was further explored by Prof. Dr. Wolfgang Friess (Technical University, Munich) who gave a very good overview of the field and its challenges. Also Dr. Joel Richard (Beaufour Ipsen industry, Dreux, France) covered the area of biopharmaceuticals, and many of the various commercial and academic drug delivery systems in development for this important class of molecules. As the final speaker of the course, Dr. Lorenz Meinel (Novartis, Switzerland) covered some of the on-going activities in the controlled release of proteins and peptides, and also gave the audience some inspiring insights into where the field may go in the future.

Written feedback from the delegates showed that this first workshop on parenteral controlled release formulations was very much appreciated by the audience, and that the course helped them in broadening their understanding of such complex formulations and their role in the pharmaceutical industry.

Hot Melt Extrusion and its use in the manufacturing of pharmaceutical dosage forms (Joint Course with AAPS)

(Written by Thorsten Schmeller)

Tarrytown, New York, April 12-13, 2011

On April 12th and 13th a seminar was held on hot melt extrusion (HME) at the Westchester Marriott and BASF Corporation in Tarrytown close to New York City and was attended by about 140 participants. It was the first event co-organized by the AAPS and APV as a part of their respective educational programs. It was chaired by Prof. Dr. Kleinebudde (University of Düsseldorf), Prof. Dr. Mike Repka (University of Mississippi), Dr. Iris Ziegler (Nycomed) and Dr. Nigel Langley (BASF Corporation). The workshop was split into four parts:

1. Lectures with theoretical and scientific focus

Prof. Repka gave a general introduction to HME in pharmaceutical manufacturing. He focused on equipment and processing, together with a few case studies. Dr. Karl Kolter, BASF, presented information on excipient requirements in HME, describing the polymer characteristics, which influence the process and the product quality. Special attention was paid to Soluplus, a new solubilizer for HME. Prof. Kleinebudde's talk covered solid lipid extrudates and the challenges in formulating them e.g. the influence of API crystal shape on extrudability. Andreas Gryczke, Thermofisher, talked about theoretical approaches and models for predicting polymer suitability including the relevant equations.

The session was concluded by two young scientists, who presented their PhD. studies. While Min Yang from the New Jersey Institute of Technology reviewed acetaminophen solubility in polyethylene oxide, Ana Almeida, University of Ghent discussed the use of ethylene vinyl acetate as a matrix former.

2. Lectures from practitioner to practitioner

Iris Ziegler talked about benefits and hurdles of HME from her experience. PD Dr. Karl Wagner, Boehringer Ingelheim, gave an insight into early development focusing on the challenges related to the availability of very small quantities of API. Michael Lowinger, Merck & Co, and Adam Dreiblatt, CPM Century Extrusion, covered scale-up in their lectures highlighting screw design, degree of fill, residence time and QbD. The focus of Prof. Khinast's, Research Center

on Pharmaceutical Engineering, talk was on continuous processing, while Prof. Vervaet, University of Ghent, concluded this session with a lecture on injection moulding.

3. Case studies

The case studies were presented by several lecturers from the industry. Representatives came from Evonik, F. Hoffmann-La Roche, Merck, Boehringer, Novartis, Bend Research, Agere and Particle Sciences and covered a wide span of HME-related topics.

4. Practical demonstrations of equipment

The demonstrations took place in the BASF laboratories, where Brabender, Gabler, Leistritz and Thermofisher showed their equipment in action. The tour also included a visit to the BASF technical center for extrusion of plastics, where about 5 extruders of different size were in operation.

The participants in particular liked the discussions with many industry experts sharing their knowledge. Overall this workshop provided a comprehensive overview of HME. A compendium handed out to all participants is also available for download from the excipients section of the BASF website at <http://www.pharma-ingredients.basf.com>.

Poorly Water Soluble Drugs: Successful Formulation Approaches (Written by Carsten Timpe)

Ludwigshafen, Germany, October 28-29, 2010

The focus of APV course No. 6336, moderated by Dr. Oskar Kalb (Roche) and Dr. Carsten Timpe (Novartis), was formulation technologies for poorly soluble drugs. This is the 3rd course that has been held on this topic in recent years. This time it took place at BASF, one of the biggest chemical companies in the world, in Ludwigshafen. The scope of the course was to provide a broad overview on `state of the art` formulation technologies (melt extrusion / solid dispersion, nanoformulations, lipid delivery systems) and included contributions from pharmaceutical polymer manufacturers which were represented by BASF and Evonik.

The course started with a general introduction to the topic by Dr. Rolf Hilfiker from Solvias, who talked about analytical characterization techniques for solubility and solid forms and on the 2nd day by Dr. Jochem Alsenz from Roche. Participants had the chance to follow a lively, practical demonstration of the different formulation systems of the lipid classification system according to Prof. Pouton, given by Dr. Matthew Leigh from Phares, Switzerland who discussed the power and the pitfalls of lipid delivery systems.

An insight into the oral and parenteral applications of cyclodextrin formulations was given by Marcus Brewster from J&J. Solid dispersions were covered by Prof. Guy van den Mooter (Catholic University Leuven) and Dr. Kathrin Nollenberger from Evonik Röhm. BASF - who hosted the seminar - was represented by two speakers: Dr. Michael Gerrit-Herting, who talked about a new high throughput robot for solubilizer screening, and Dr. Hendrik Hardung who covered hot melt extrusion from the aspect of excipient selection. The topic of nanomilling was presented by Dr. Michael Juhnke from Novartis Basel, while parenteral formulations for poorly soluble drugs were discussed by Dr. Bernd Riebesehl from the same company. Biopharmaceutical aspects of these formulation approaches were presented in two lectures by Dr. Stefan Willmann from Bayer Technology Services, who described applications of PK-SIM software and by Dr. Oskar Kalb from Roche, who gave an overview of PK variability after oral administration together with practical formulation examples proven to reduce it.

At the end of the first day participants toured the huge BASF site in Ludwigshafen by bus. The tour gave them a good impression not only about the size of the area which includes three Rhine harbours and a power station big enough to deliver power to half of the population of Berlin, but also BASF's commitment to the efficient use of all side products from the production processes, thus, illustrating the increasingly "green" mindset of the big chemical industry in Europe.

DRUG DELIVERY PRODUCTS

Provided by Dr. Louise Rosenmayr-Templeton

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Viramune® XR™ (nevirapine) (Boehringer Ingelheim)

In March 2011 the US Food and Drug Administration (FDA) approved Viramune® XR™ (nevirapine) extended-release tablets for the treatment of adults with HIV-1 infection [1]. The product should only be used in combination with other anti-retroviral therapies. Nevirapine is a non-nucleoside reverse transcriptase inhibitor whose most serious side-effects include hepatotoxicity and skin reactions. In order to reduce the incidence of rash in nevirapine-naïve individuals, patients are first treated with Viramune immediate release tablets (200 mg once daily) for 14 days before being transferred on to the hypromellose-based sustained release formulation containing 400 mg of active. This wash-in period does not apply to patients already stabilized on the twice daily dose of the immediate release formula.

Approval was based on 48-week data from an ongoing, randomized, double-blind, double-dummy, active controlled Phase 3 trial (VERxVE study) in treatment-naïve subjects that compared the efficacy and safety of VIRAMUNE XR 400 mg once daily versus VIRAMUNE 200 mg twice daily. The VERxVE study demonstrated the non-inferiority of the sustained release product compared with the immediate release one with respect to suppression of viral levels and safety profile. The results of this trial are supported by 24-week data from an ongoing, randomized, open-label trial in patients who had been taking Viramune 200 mg twice daily for some time prior to joining the study

Bydureon™ (exenatide) (Eli Lilly Nederland B.V.)

At its April meeting the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that Bydureon 2 mg, powder and solvent for prolonged-release suspension for injection, receive marketing authorization within the EU [2]. This product is an intramuscular injection of exenatide, a glucagon-like peptide 1 (GLP-1) receptor agonist, for weekly administration. It is indicated for the treatment of Type 2 diabetes in combination with certain oral therapies in adults whose blood sugar is inadequately controlled by maximally tolerated doses of the aforementioned oral therapies. Exenatide was first approved in the EU in 2006 as a twice daily injection under the trade name Byetta® [3].

Bydureon is the result of a collaboration between Amylin Pharmaceuticals, Eli Lilly and Alkermes and uses Alkermes' Medisorb® technology (poly(lactide-co-glycolide) microparticles) to achieve sustained release of the peptide. The CHMP recommendation for approval was based on data from studies in the DURATION clinical program in which Bydureon administration resulted in a statistically significant reduction in A1C (a measure of average blood sugar over three months) of between 1.5% - 1.9% percent after six months [4].

The recommendation is a welcome boost for the three companies as in 2010 the product received two complete response letters from the FDA. The first letter, received in March 2010, included questions with regard to product labeling, the Risk Evaluation and Mitigation Strategy (REMS) and existing manufacturing processes. The second, which followed in October 2010, included a request for a detailed QT (tQT) study with exposures of exenatide higher than typical therapeutic levels. It was based on concerns about drug accumulation in the body [5]. The companies intend to reply to the second request in late 2011.

References and Further Information

- [1] Entry on Viramune XR on Drugs@FDA
http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201152s000lbl.pdf (Accessed on 3.5.2011)
- [2] Committee for medicinal products for human use (CHMP) Summary of Opinion on Bydureon
http://www.ema.europa.eu/docs/en_GB/document_library/... (Accessed on 29.4.2011)
- [3] Entry for Byetta on the European Medicines Agency website
<http://www.ema.europa.eu/ema/...> (Accessed on 29.4.2011)
- [4] BYDUREON™ Recommended for Approval in Europe. Press release on Alkermes website.
<http://investor.alkermes.com/phoenix.zhtml?...> (Accessed on 1.5.2011)
- [5] Amylin, Lilly and Alkermes Announce Receipt of Complete Response Letter from FDA for BYDUREON™. Press release on Alkermes website.
<http://investor.alkermes.com/phoenix.zhtml?...> (Accessed on 1.5.2011)

DRUG DELIVERY TERMINOLOGY

Provided by Dr. Karsten Cremer

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DISINTEGRATION

The process by which a dosage unit visibly disintegrates

[Write a comment on this definition](#)

The disintegration of tablets and capsules in an aqueous medium is an important quality parameter for immediate release formulations. It is tested with a specific apparatus prescribed by the pharmacopoeias. Disintegration should not be confused with dissolution: It is possible that a tablet rapidly breaks up into its primary particles from which it has been compressed without any significant dissolution. Vice versa, a controlled release dosage form may not disintegrate at all before all its active ingredient has been released in dissolved form.

DISSOLUTION

The process by which an active ingredient is released in dissolved form from a dosage unit

[Write a comment on this definition](#)

The dissolution profile of a formulation is a particularly important quality feature of any drug formulation. In fact, the biological performance of a formulation is to a considerable degree determined by the dissolution behaviour. Dissolution is tested *in vitro* using one of the apparatus prescribed in the major pharmacopoeias, possibly using various types of aqueous media. It should however be noted that the dissolution profiles obtained *in vitro* may differ substantially from the dissolution behaviour *in vivo*.

[Suggest a term to be defined](#)

[Suggest a definition](#)

Provided by Jeffrey Grunkemeyer

ACINO (Headquarters in Basel, Switzerland)

Founded:	Schweizerhall was founded in the first half of the 19 th century. It acquired Cimex AG in 2005 and Novosis AG in 2006; the new entity was renamed ACINO in 2008.
Location:	Headquarter: Basel (CH). Development / manufacturing sites: Liesberg (CH) and Miesbach (DE)
Ownership:	Public, quoted as ACIN on the Swiss stock exchange
Employees:	Number of employees: 440
Key technology:	Acino is specialized in the development, registration and manufacture of pharmaceuticals using advanced drug delivery technologies for which Acino holds some patents. Acino's focus is on (i) solid oral dosage forms with modified release of the active ingredient, using pellet or matrix formulations, (ii) transdermal therapeutic patches, (iii) biodegradable subcutaneous implants, and (iv) oral dispersible formulations, e.g. films and tablets.
Products:	Acino has developed a range of products with a «formulation plus». It assembles complete registration dossiers, offers for all products a Common Technical Document (CTD), and supplies leading pharmaceutical companies with its products throughout Europe. A list of Acino's current product offerings is provided on the website.
Development status:	Acino works on numerous development projects, either as a partner of the international pharmaceutical industry or on its own initiative to develop projects which will be available for licensing. Currently the pipeline comprises 18 projects, of which several are in late stage development or awaiting approval. A more complete description of Acino's development pipeline is provided on the company's website.
Partnerships:	Acino possesses a vast spectrum of technologies for modified drug release and deploys its expertise and ability to optimize the therapeutic benefit of pharmaceuticals or improve the drug delivery system as compared to the corresponding originator drug. Acino offers its partners from the pharmaceutical industry a comprehensive spectrum of services, ranging from the sourcing of active ingredients, initial feasibility studies, full product development, registration and manufacturing to final packaging and logistics. One of Acino's current partners is Bayer Schering Pharma, with whom they are developing a novel contraceptive patch, currently in Phase III.
Website:	http://www.acino-pharma.com
Contact:	Dr. Jean-Daniel Bonny (Global Head R&D) Acino Pharma AG Erlenstrasse 1 CH-4058 Basel Switzerland Phone: +41 - 61 - 338-6091 e-mail: jean-daniel.bonny@acino-pharma.com

DRUG DELIVERY PEOPLE

Provided by Prof. Dr. Karsten Mäder

PROF DR. ALEXANDER KABANOV is a Parke-Davis Professor of Pharmaceutical Sciences and Director Center for Drug Delivery and Nanomedicine, University of Nebraska Medical Center. He received his Ph.D. degree in chemical kinetics and catalysis in 1987 at Moscow State University (MSU), USSR. Prior to joining the University of Nebraska in 1994, he pioneered use of polymeric micelles and DNA/polycation complexes for drug and gene delivery. He co-founded Supratek Pharma, Inc., Montreal, Canada, which develops therapeutics for the treatment of cancer. He leads the field of "polymer genomics" that investigates effects of polymers and nanomaterials on cellular responses to develop safe and efficient therapeutics. Over 200 scientific papers and over 26 US patents worldwide have been published by him. His work has been cited over 9,000 times (Hirsh index 54).

He founded the Nanomedicine and Drug Delivery Symposium series (2003-) and co-chaired the Gordon Research Conference on Drug Carriers in Medicine and Biology (2006). He is a recipient of the Lenin Komsomol Prize (1988), the NSF Career Award (1995), the University of Nebraska ORCA Award (2007), UNMC Scientist Laureate (2009), and the Russian "Megagrant" (2010) among other distinctions. He is a Director of the NIH Center of Biomedical Research Excellence (CoBRE) the "Nebraska Center for Nanomedicine", and visiting Professor and Director of the Laboratory of Chemical Design of Bionanomaterials at MSU.



This new newsletter section is intended to give a brief overview of academic groups based at European Universities. In this issue the focus is on groups working on transdermal technology research. It is the first of an occasional series reviewing the work of research groups exploring different aspects of drug delivery research. It is not intended to be a comprehensive list of those involved in the area but give our readers a flavour of the groups involved. As it is a living document, our readers are most welcome to suggest other transdermal research teams they are aware of for inclusion in our next edition. [Contact](#)

Bath

Institution	United Kingdom, Bath: University of Bath
Group	The Department of Pharmacy and Pharmacology
Key contact	Prof. Richard H. Guy
Website	http://www.bath.ac.uk/pharmacy/staff/rhg2.html
E-Mail	r.h.guy@bath.ac.uk
Research areas	<ul style="list-style-type: none"> • Topical bioavailability of drugs and other skin-active species • Mechanisms of iontophoretic drug delivery across skin • Prediction and assessment of dermal exposure

Braunschweig

Institution	Germany, Braunschweig: Technische Universität Carolo-Wilhelmina
Group	Institut für Pharmazeutische Technologie
Key contact	Prof. Dr Christel Müller-Goymann
Website	http://www.pharmtech.tu-bs.de/
E-Mail	c.mueller-goymann@tu-bs.de
Research areas	<ul style="list-style-type: none"> • Colloidal drug delivery systems – Development and characterization • Penetration / Permeation into human skin • Cell cultivation methods for permeation studies

Erlangen

Institution	Germany, Erlangen: Friedrich-Alexander-Universität
Group	Division of Pharmaceutics
Key contact	Prof Geoffrey Lee, Chair of Pharmaceutics
Website	http://www.pharmtech.uni-erlangen.de/
E-Mail	lee@pharmtech.uni-erlangen.de
Research areas	<ul style="list-style-type: none"> • Solubility and release • Thermodynamic activity concepts in polymeric matrices • Needle free injection

Geneva

Institution	Switzerland, Geneva: University of Geneva School of Pharmaceutical Sciences
Group	Skin Bioengineering Group
Key contact	Dr. Yogeshvar N. Kalia
Website	http://www.unige.ch/sciences/pharm/sbg/kalia-STG.html
e-Mail	yogi.kalia@unige.ch
Research areas	<ul style="list-style-type: none"> • Development of new formulations for topical delivery • Investigating the iontophoretic transport of peptides and proteins across the skin –non-invasive delivery of therapeutic molecules and the elucidation of structure-transport relationships • Development of minimally-invasive technologies for transdermal delivery of macromolecules – proteins and antibodies. • Modification of drug structure and molecular properties to design therapeutics better suited to transdermal administration.

Halle

Institution	Germany, Halle-Wittenberg: Martin-Luther-Universität
Group	Pharmazeutische Technologie und Biopharmazie/ AG Biopharmazie
Key contact	Prof. Dr. Reinhard Neubert
Website	http://pharmtech.pharmazie.uni-halle.de/deutsch/ag-biopharm/
E-Mail	neubert@pharmazie.uni-halle.de
Research areas	<ul style="list-style-type: none">• Barrier function of stratum corneum• Stratum corneum lipids and their interference (e.g. ion-pairs)• Institut für Angewandte Dermatopharmazie (w. Prof. W. Wohlrab)

Hamburg

Institution	Germany, Hamburg: Universität Hamburg
Group	Lehrstuhl für Pharmazeutische Technologie
Key contact	Prof. Dr. Claudia S. Leopold
Website	http://www.chemie.uni-hamburg.de/pha/phatech/mitarbeiter/leopold.html
E-Mail	Claudia.Leopold@uni-hamburg.de
Research areas	<ul style="list-style-type: none">• Quantification and optimisation of the penetration of actives through the skin

Leiden

Institution	The Netherlands, Leiden: Leiden/Amsterdam Center for Drug Research
Group	Drug Delivery Technology – Skin Research Group
Key contact	Prof. Dr. Joke Bouwstra
Website	http://ddt.lacdr.gorlaeus.net/people/bouwstra
E-Mail	bouwstra@lacdr.leidenuniv.nl bouwstra@chem.leidenuniv.nl
Research areas	<ul style="list-style-type: none">• Stratum corneum substitute research• Dermal vaccine delivery with elastic vesicles• Lipid organization in healthy and diseased skin• Optimisation and application of human skin equivalents• (Pro)drugs for iontophoretic delivery

London

Institution	United Kingdom, London: University of London
Group	The School of Pharmacy
Key contact	Dr. Majella Lane / Prof. em. Dr. Jon. Hadgraft
Website	http://www.pharmacy.ac.uk/majella_lane.html
E-Mail	majella.lane@btinternet.com
Research areas	<ul style="list-style-type: none">• Transdermal and topical drug delivery• Mechanisms of penetration enhancement• Percutaneous absorption

Parma

Institution	Italy, Parma: Università degli studi die Parma
Group	Dipartimento Farmaceutico
Key contact	Prof. ssa Patrizia Santi
Website	http://www.unipr.it/arpa/dipfarm/
E-Mail	patrizia.santi@unipr.it
Research areas	<ul style="list-style-type: none">• Mechanisms involved in iontophoretic drug transport (passive diffusion, electro-transport and electroosmosis),• Iontophoretic delivery of peptides and proteins,• Reverse iontophoresis for diagnostic purposes and• Realization of innovative transdermal drug delivery systems.

Disclaimer: Although every effort has been made to check the accuracy of the contents of the tables, including contacting the groups involved, there may be some inaccuracies and/or omissions.

FEATURED ARTICLE

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THE ÉLAN OF DELIVERY TECHNOLOGY DEVELOPMENT

By Louise Rosenmayr-Templeton, Ph.D., Tower Pharma Consulting, Auhofstrasse 197/10, A-1130 Vienna

1. Introduction

On 9 May 2011 it was announced that Alkermes Inc. (Waltham, MA, USA) and the Elan Corporation plc (Dublin, Ireland) had signed an agreement under which Alkermes would merge with Elan Drug Technologies (EDT), the drug delivery division of the Elan Corporation [1]. The cash and stock transaction is valued at US \$960 with Elan receiving US \$500 million cash plus an around 25 % stake in the new company to be named Alkermes plc and headquartered in Ireland. The deal, which at the time of writing this article, was still subject to the approval of Alkermes shareholders, regulatory go-ahead and customary closing conditions, creates a company with over 25 commercialised products and a pipeline of proprietary and partnered products. The focus will be on products for the treatment of diseases of the Central Nervous System which fits with the portfolios of both parties to the merger.

Although the Elan Corporation's 25 % stake in Alkermes plc means that it has not completely divorced itself from the world of drug delivery, it is to an extent the end of an era. That era began in Ireland in 1969 when the American entrepreneur, Donald Panoz, founded the company, which was then solely focused on improving the oral delivery of established drugs through the development of novel formulation technologies

This short review article looks back at the company's contribution to therapeutic delivery in terms of technologies currently used in commercialized or late stage clinical products. It includes some technologies that are no longer part of the Elan portfolio but were spun-out or sold to other companies. In the interest of brevity I have deliberately excluded technologies which were owned by the company for a short time. These include those developed by the former Quadrant Healthcare (through the acquisition of Innovata plc now part of the Ventura Group [2, 3]) and The Liposome Company whose Abelcet® product is now sold by Sigma Tau Pharmaceuticals Inc. [4]. The article also looks briefly at some of the start-up companies that came into being following Elan's financial difficulties in 2002/2003.

2. Technologies Currently within the Elan Drug Technologies Portfolio

2.1 NanoCrystal® Technology

NanoCrystal® technology, is Elan's particle size reduction technology to increase the solubility of poorly-soluble drugs [5-7]. This technology did not originate within Elan itself, but was initially developed by NanoSystems LLC, a subsidiary of Eastman Kodak [8]. It employed Eastman's expertise in milling pigments to develop a wet milling and particle stabilization technology to reduce the size of drug particles to less than 2000 nm and maintain their physical stability over time. Stabilisation against agglomeration is achieved by absorbing selected GRAS (Generally Regarded As Safe) stabilizers to the surface of the particles. The resulting solution can be further processed and incorporated into a variety of dosage forms.

It was in the late 1990s that it became apparent that this technology showed great promise in improving the bioavailability of drugs whose solubility was dissolution-rate limited. In September 1998 Elan bought NanoSystems from Eastman Kodak for US \$150 million [8]. The NanoCrystal technology is Elan's most successful delivery technology and is the basis of 5 marketed products which generated US \$1.9 billion plus in annual in-market sales in 2010. These include Rapamune® Tablets (Wyeth, now Pfizer), Megace® ES Suspension (Strativa Pharmaceuticals), Emend® Capsules (Merck) and Tricor® 145 Tablets (Abbott Laboratories). Use of the technology has in some cases not only improved bioavailability, but also allowed dose reduction (Tricor® 145) and/or removed or reduced the effect of food on drug absorption

(Megace ES, Emend). In addition, its employment can reduce time to onset of action by increasing the rate of absorption and allow the development of smaller or more convenient dosage forms (Rapamune, Megace ES). It has been recently applied to the development of a sustained release injectable, Invega Sustenna (US)/Xeplion® (Europe) demonstrating that the technology is applicable to parenteral products. The technology is protected by over 1,200 patents/patent applications in U.S. and rest of the world [5-7].

2.2 SODAS® (Spheroidal Oral Drug Absorption System)

SODAS is a multiparticulate system for controlling the release of drugs taken orally [5-7]. It is based on the coating of uniform spherical sugar beads of 1-2 mm in diameter with drug and excipients. These drug loaded beads are then coated with controlled release polymers (water soluble and insoluble, pH dependent/independent) to form a release rate controlling membrane. Finally the beads are filled into hard gelatin capsules for ease of administration. Depending on the coating polymers chosen, different release profiles can be achieved. In addition, beads with different release profiles or actives can be incorporated into the same capsule. This allows for tailored profiles including immediate release followed by sustained, pulsatile or delayed release.

SODAS is one of Elan's oldest and most successful technologies and was used in Cardizem® SR (a twice daily formulation of diltiazem) which the company developed for Merrill Dow and which was approved by the FDA in 1989, and Cardizem® CD (once daily formulation of diltiazem) as a classic life cycle management strategy in 1991 [9]. More recently it has been used to achieve sustained delivery of morphine from a once daily formulation marketed under the trade name Avinza® [5]. This product also provides the patient with fast relief as the formula is designed to release a proportion of the drug immediately. SODAS technology has also been used to develop Ritalin® LA (methylphenidate with a bi-modal release profile); Focalin® XR, an extended release formulation of dexamethylphenidate hydrochloride also with a bimodal release profile; Luvox® CR, a formulation which allows once daily dosing of fluvoxamine maleate and Zanaflex® Capsules [6].

2.3 IPDAS® (Intestinal Protective Drug Absorption System)

This technology involves high density drug loaded beads compressed to form controlled release tablets [5-7]. It is particularly suitable for compounds that are gastro-irritant due to the fact that the tablet rapidly disintegrates following ingestion dispersing the controlled beads so that no one part of the gastrointestinal tract is exposed to a very high local concentration of drug. The technology is based on extruded and spheronised multiparticulates with release being controlled by the nature of the drug-containing bead matrix or its semi-permeable membrane coating or both. It was initially designed for a proprietary formulation of naproxen with fast onset of action followed by pain relief over a 24-hour period which is marketed in the US and Canada under the trade name, Naprelan®.

2.4 CODAS® Technology (Chrono-therapeutic Oral Drug Absorption System)

This technology is designed to delay drug release for a predetermined time to tune therapy to the body's circadian rhythms while providing patients with the convenience of reduced dosing [5-7]. It is used in Verelan® PM, a once daily antihypertensive therapy which is dosed at night. The formulation is designed to delay onset of action for 4 hours so that the risk of early morning cardiovascular events is minimized. Verelan® PM was first launched in 1998 in the US and is now marketed by UCB Pharma [5].

Again, the technology is based on polymer coated multiparticulates. However, in the case of CODAS, the delay in release is controlled by the level of the release controlling coating which consists of a mixture of water-soluble and insoluble polymers. The delay is determined by the dissolution of the water-soluble polymers which occurs slowly when the beads come into contact with gastric and/or intestinal fluids. Release following the initial delay is controlled by pores in the membrane formed by the insoluble coating components.

2.5 MXDAS® Technology (MatriX Drug Absorption System)

Unlike a number of other Elan technologies, MXDAS is based on a hydrophilic matrix tablet composed of a proprietary blend of polymers which releases drug due to a combination of diffusion and erosion [5-6]. The tablets can be produced by direct compression or granulation and be enteric coated if required. It was used to develop a sustained release formulation of dalfampridine for Acorda Therapeutics. This product was approved by the FDA in January 2010 under the trade name Ampyra® to improve walking ability in Multiple Sclerosis patients [5-6]. The product, subsequently licensed to Biogen Idec, ex US, was recommended for conditional approval in Europe by the Committee for Medicinal Products for Human Use (CHMP) in May 2011.

2.6 PRODAS® (Programmable Oral Drug Absorption System)

The PRODAS technology is based on a hybrid of multiparticulates and hydrophilic matrix technologies to produce mini-tablets that are filled into a capsule [5-7]. Using this technology it is possible to combine mini-tablets with different release profiles or sizes within the one capsule in order to achieve high drug loading and a very smooth and constant release profile throughout the GI tract. The rate of drug dissolution from the individual mini-tablets depends on the nature of the matrix (immediate, delayed or sustained release) and the presence or absence of a rate-controlling coating.

2.7 DUREDAS™ Technology (Dual Release Drug Absorption System)

DUREDAS, as the name would suggest, is a bilayer tablet. It therefore can be used to provide immediate or sustained release of two drugs or different release rates of the same drug in one dosage form [5-6]. The DUREDAS™ technology was initially developed for OTC controlled release analgesics. In this case one layer of the tablets was formulated as an immediate release granulate to achieve rapid onset of action, while the second released the drug slowly to provide sustained pain relief.

2.8 Other Technologies

The PharmaZome® and INDAS™ technologies were developed by Elan but are no longer actively promoted [6]. PharmZome consisted of drug-loaded microparticles in the size range 5 to 125 microns produced by either spray drying or emulsion techniques. They could be used for taste-masking and/or to achieve controlled or delayed release, while their particle size range conferred good mouth-feel and enabled their incorporation into formulations such as chewable and effervescent tablets and powders for reconstitution [10].

INDAS technology (Insoluble Drug Absorption System) was a method of improving drug solubility by converting an active into the amorphous form by a combination of energy, excipients and processing and stabilising it using a cross-linked polymer [10]. It was superseded by the NanoCrystal technology.

3 Technologies Developed in Part by Elan

This section deals with some technologies that were initially or partially developed within Elan or its joint ventures but are no longer part of its portfolio. Most of these technologies were divested in the wake of a dramatic fall in the company's share price following the US Securities and Exchange Commission's launch of an investigation into the company's accounting practices in 2002. As before, only technologies that have been commercialized or are in late clinical development have been included.

3.1 Transdermal Systems

Prior to 2003 Elan had a long association with transdermal delivery systems. It developed one of the first nicotine patches, Prostep®, which was approved in 1992 [11]. It had a fully owned subsidiary, Elan Transdermal Technologies Inc. (ETT), which employed 100 staff and was able to provide clients with research, development, clinical trial manufacture and commercial production services. In 2003 ETT was sold to Nitto Americas Inc., the US subsidiary of the Japanese giant, Nitto Denko. It still operates under the name Aveva Drug Delivery Systems (Miramar, Florida) [12].

3.2 GIPET™ (Gastrointestinal Permeation Enhancement Technology)

Merrion Pharmaceuticals Ltd (Dublin, Ireland) was set up in 2004 to develop technologies based on permeation enhancement that it had acquired from Elan for oral peptide and small molecule delivery. Isis licensed similar technology from Elan for oral gene delivery [13, 14]. As a result of advancements on the original Elan technology, GIPET, is now the basis of the company's pipeline of oral products, and the subject of a number of licensing and collaboration agreements with companies such as Novo Nordisk [15].

GIPET is based on the production of enteric coated tablets or capsules containing drug formulated together with medium chain fatty acids (typically sodium caprate) or medium-chain fatty acid derivatives or microemulsion systems based on medium-chain fatty acid glycerides [16]. It has been shown to act as a permeation enhancer and improve the bioavailability of Biopharmaceutical Classification System Class 3 compounds less than 10kDa in size i.e. those with good aqueous solubility but poor membrane permeability [17]. These include alendronate, low molecular weight heparin and insulin [16]. The enteric coating of GIPET dosage forms protects the active from degradation and prevents active and enhancer release until the dosage form has reached the small intestine. Once in the more alkaline environment of the duodenum, both drug and enhancer are released simultaneously. The enhancer has been shown to improve the oral bioavailability of a variety of poorly permeable compounds by a factor of 10 to 50 [15]. The enhancer probably improves bioavailability by a number of mechanisms including mixed micelle formation and direct effects on the intestinal wall such as the dilation of tight junctions [16, 18].

Concerns that these effects might lead to long-lasting mucosal toxicity and result in accidental absorption of bacteria present in the gut appear unfounded with studies carried out by Prof David Brayden (University College Dublin and ex-Elan) and his team showing that sodium caprate did not increase the permeation of *S. typhimurium* across isolated rat intestinal ileal mucosae [19]. In addition, the effects of the enhancer have been shown to be short-lived in humans with intestinal permeability returning to normal within 40 minutes, as demonstrated by the absorption of intra-jugally administered polar sugars such as mannitol that are only absorbed via the paracellular route [16, 18].

Merrion's lead product, Orazol™, is a once-weekly tablet formulation of the anti-cancer bisphosphonate, zoledronic acid. This drug is currently only available as an injectable product which must be infused once monthly [15]. Orazol is about to enter a Phase III study that will compare its safety and efficacy as an adjuvant in the treatment of breast cancer to placebo. The company is also investigating Orazol for the treatment of bone metastases. The company's own pipeline also includes a new formulation of alendronate, acyline (an oral GnRH antagonist) and MER-102 (an ultra low molecular weight heparin). Merrion also has partnered compounds with amongst others Novo Nordisk (insulin, GLP-1 analogue and one other), Ferring Pharmaceuticals, Rebel Pharma and a top ten Pharma (3 compounds) [15].

3.2 Nobex Joint Venture and Oral Peptides

The Nobex Corporation had a proprietary technology to enable the oral delivery of proteins, peptides and small molecule drugs. It was based on the conjugation of oligomers, such as polyethylene glycol moieties, to compounds to protect them from degradation and improve their absorption across the gut mucosa [20]. It formed a joint venture with Elan called Synerobex which, in 2002, took an oral calcitonin product for the treatment and prevention of osteoporosis into a Phase 1 clinical trial [21]. In 2006 Biocon Ltd (Bangalore, India) acquired Nobex's 300 plus patent estate for US\$ 5 million after the company went bankrupt [22]. Biocon continues to develop an oral insulin product based on recombinant human insulin covalently conjugated to a monodisperse, short-chain methoxypolyethylene glycol derivative [23, 24].

3.4 The Iomai Joint Venture and the Needleless Patch

Elan had a joint venture with the Iomai Corporation (Washington, USA) called the Xairo Corporation Ltd and for a number of years had a financial stake in the company. The JV centered around the use of Elan's transdermal patch technologies in combination with Iomai's transcutaneous vaccination expertise. The successful JV had a number of products in clinical trials [25]. Iomai was bought by Intercell AG (Vienna, Austria) for US \$189 million in 2008 [26]. The needleless patch technology can be used to deliver antigens of any size and/or adjuvants (in the form of a vaccine enhancement patch) to Langerhans cells of the dermis. The skin is first abraded to remove the top layers of the stratum corneum before applying the patch. The technology has been assessed in Phase III clinical trials with a vaccine for Traveler's Diarrhea, which unfortunately failed to show efficacy. Development of this product was stopped in December 2010 but Intercell are continuing to use the technology to develop a pandemic low dose influenza patch (in Phase I/II) [26].

4 Start-Ups

A number of new companies were set up in the wake of the job losses and divestitures that occurred in Elan in 2002/2003. A number of these are listed below:

Athpharma Ltd was founded in 2001 by John Devane, the former Executive Vice President of Research & Development at Elan, plus two other former Elan executives, John Kelly and Paddy Ashe [27]. It specialized in developing formulations and isomers of established drugs for the treatment of cardiovascular and gastrointestinal diseases. In 2005 it was sold to Seamus Mulligan, the former Chief Technology Officer of Elan. Its assets are now part of **Circ Pharma**, another specialty pharma company focused on the development of new formulations of cardiovascular and CNS/pain medication using chronotherapeutic technology [28]. Margot Foynes, the Chief Technical Officer at Circ, was previously senior director of project management at Elan.

John Devane then established a further company **AGI Therapeutics** together with Paddy Ashe, and were joined by Mary Martin, former managing director of Elan Biotechnology Research. AGI initially focused on reprofiling molecules for gastrointestinal disorders. It had a lead compound, Rezular, for irritable bowel syndrome which failed in Phase III in 2009 [29, 30]. The company is now developing new therapies for critical care, including an inhaled formulation of a treatment for a life-threatening, lung-related, condition [31].

In addition to Circ Pharma, Seamus Mulligan is also CEO of **Azur Pharma** [32], a private company which markets prescription products through three US-based specialty sales forces, two in CNS and the other in Women's Health. It also has a number of development programs to manage the product life cycle of certain compounds.

BioClin Research Laboratories based in Athlone, Ireland was set up by Mary Burke (responsible for clinical pharmacology at Elan) and the late Brian McKenna (manager of Elan's bioanalytical laboratory) to provide analytical and bio-analytical services to the pharmaceutical, drug delivery and medical device industries [29]. In February 2008 it was taken over by Intertek and operates as Intertek BioClin Laboratory (Ireland) [33].

The venture capital healthcare fund **Fountain Healthcare Partners** was founded by three members of the Elan corporate venture capital group: Manus Rogan, Aidan King, and Ena Prosser plus a fourth partner, Justin Lynch [34]. The focus of the fund is on life sciences and in particular specialty pharma, medical devices, biotechnology and diagnostics. Companies funded by Fountain include Palyon Medical Corporation, a medical device company developing programmable implantable pumps for delivery to the intrathecal space, and the Amarin Corporation which develops therapeutics for the treatment of cardiovascular and CNS disorders.

5. Back to the Future

This short article only gives a flavour of Elan's impact, past and present, on the field of drug delivery. It is to be hoped that this legacy continues within the new Alkermes and that the skills of both parties to the merger are synergistic in producing not only "a portfolio of products and pipeline based on proprietary science and technologies" [1] but also new technologies to meet the therapeutic delivery needs of tomorrow.

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DRUG DELIVERY LITERATURE

Provided by Dr. Karsten Cremer

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Our mission includes in particular the following tasks:

- Thoroughly understanding the physical-chemical and biopharmaceutical properties of the drug substance to be delivered and the components of the drug delivery system
- Understanding the biological barriers and the interactions of the drug molecule and its delivery system with the biological environment and the biological target including PK/PD and PK/safety relationships
- Research on excipients, materials and technologies required for the design, preparation and manufacturing of drug delivery systems for a selected route of administration
- Development and understanding of methods for in vitro and in vivo evaluation of drug delivery systems and their components
- Knowledge of regulatory requirements for clinical testing, manufacturing and registration of drug delivery systems

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