APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER ISSUE 2/2013

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DRUG DELIVERY EVENTS

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Provided by Christoph Blümer

40th Annual Meeting & Exposition of the Controlled Release Society
July 21-24, 2013, Honolulu, Hawaii, U.S.A. — Details

APV Course 6520: Highly potent drug compounds - Development and manufacturing of oral drug products
September 04-05, 2013, Heidelberg, Germany — Details

APV Course 6505: Formulating better medicines for children - Meeting the needs of the children 5th conference of the European Paediatric Formulation Initiative
September 18-19, 2013, Barcelona, Spain — Details

Suggest a meeting to be announced!

APV COURSE SUMMARIES

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SUCCESSFUL EARLY STAGE DEVELOPMENT OF PHARMACEUTICALS

By Dr. Louise Rosenmayr-Templeton

The APV course "Successful Early Stage Development of Pharmaceuticals" was held in Darmstadt, Germany on 5th and 6th March 2013. The chairs were Dr. Mathew Leigh, biorelevant.com, Croydon, UK and Dr. Louise Rosenmayr-Templeton, Tower Pharma Consulting, Vienna, Austria. The course focused on the development of small molecules from lead selection to Phase I and was characterized by lively contributions from both speakers and participants.

Day 1 started with two talks on selecting a good lead and early considerations for dosage form development from a Big Pharma and small company perspective from Dr. Marcus Brewster (Johnson & Johnson, Beerse, Belgium) and Dr. Robert Harris (Molecular Profiles Ltd, Nottingham, UK) respectively. This was followed by a talk from Dr. Robert Hett (RPD Rapid Pharma Development, Unterägeri, Switzerland) on the importance of getting the drug substance manufacturing process on track. The afternoon session focused on biopharmaceutical aspects and began with a presentation from Dr. Stefania Beato from Novartis (Basel, Switzerland). She discussed the biopharmaceutical classification of compounds and its implications for further development. Prof. Chris Frampton (Pharmorphix, Cambridge, UK) then focused on polymorphs, the challenges they represent to development and the importance of their early detection and characterization. This talk was followed by one from Prof. Jennifer Dressman (University of Frankfurt, Germany) on the use of biorelevant media to bridge the testing of formulations in preclinical development and the clinic. Dr. Christoph Saal (Merck, Darmstadt, Germany) then presented on salt and co-crystal selection and its impact on formulation. The first day was rounded off by

a talk from Dr. Sebastian Ullrich (Grünenthal, Aachen, Germany) in which he presented the challenges of developing intravenous formulations for preclinical and toxicological testing.

Day 2 started with a talk on permeability aspects from Dr. Eleonore Haltner-Ukomadu, Across Barriers, Saarbrücken, Germany. This was followed by a series of talks on formulation strategies for poorly water-soluble compounds. They included talks on lipid systems from Dr Anette Müllertz, University of Copenhagen, Denmark and crystalline nanoparticles from Prof. Jouni Hirvonen, University of Helsinki, Finland. Dr. Cristina Freire, Kuecept Ltd. Hertfordshire, UK spoke on amorphous systems and shared her interest in the factors affecting GI absorption with the audience. The last part of the course considered the issues for moving forward to Phase I. Dr. Jon Sutch, Patheon, Milton Abingdon, UK discussed what to focus on from a technical viewpoint and Prof. Johannes Bartholomäus, Pharmakreativ Consulting, Aachen, Germany presented on the key points to be included in a Phase I CMC submission.

DRUG DELIVERY STRATEGIES FOR POORLY WATER-SOLUBLE DRUGS - ESTABLISHED PLATFORM TECHNOLOGIES & RECENT INNOVATIONS

By Dr. Carsten Timpe

The APV course "Drug Delivery Strategies for Poorly Water Soluble Drugs - Established Platform Technologies & Recent Innovations" was held in Braunschweig, Germany on November 29/30 2012 and was chaired by Dr. Oskar Kalb and Dr. Carsten Timpe from F. Hoffmann-La Roche AG (Basel). It was the latest workshop in an ongoing series of APV courses in that field which started circa one decade ago. This time the event had its key focus on nanomilling aspects, starting with an overview presentation by Prof. Heike Bunjes (Technical University Braunschweig) and continuing with a lecture from Dr. Michael Juhnke from Novartis Pharma (Basel) on formulation development of nanoparticulates. One course highlight was the visit to the nanomilling facility at the Institute for Particle Technology at the Technical University Braunschweig led by Prof. Arno Kwade. Other course topics presented included solid dispersion development and production aspects presented by Prof. Guy van den Mooter (Catholic University of Leuven, Leuven, Belgium), which was further expanded upon by presentations from Dr. Karl Kolter (BASF AG, Ludwigshafen) about the properties of polymers for amorphous systems and the application of atomic force microscopy (AFM) to characterize these systems by Dr. Matthias Lauer (F. Hoffmann-La Roche, Basel).

Parenteral drug delivery of poorly soluble drugs was presented by Dr. Bernd Riebesehl, Novartis Basel, an unusual foam technology for poorly soluble drugs by Dr. Susanne Page and Angela Sprunk (F. Hoffmann La Roche, Basel) and the field of lipid systems was represented by a presentation from Dr. Simone Wengner (Catalent Pharma Solutions, Eberbach). Lectures focusing on the *in-vivo* PK aspects of poorly soluble drugs were given by Dr. Dieter Becker (Novartis, Basel) and as a closing presentation by Prof. Peter Langguth (University Mainz). The former featured a new electronic capsule to investigate absorption in depth.

DRUG DELIVERY PRODUCTS

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Provided by Dr. Louise Rosenmayr-Templeton

TOBI® Podhaler (Novartis)

On 22nd March 2013 the FDA approved TOBI® Podhaler, tobramycin inhalation powder, for the treatment of Pseudomonas aeruginosa infections in cystic fibrosis patients [1-3]. This product delivers tobramycin in a hand-held dry powder inhaler which has numerous convenience advantages over the existing solution for nebulization, the most significant of which is an approximate 70% reduction in treatment time per cycle [3]. The inhaler is not approved for use in children less than 6 years of age, those with forced expiratory volume in 1 second (FEV1) <25% or >80%, or in patients colonized with Burkholderia cepacia as its safety and efficacy in such patients has not been demonstrated.

The tobramycin inhalation powder, which is formulated using Novartis PulmoSphere™ technology, is filled into hypromellose capsules containing 28 mg drug for use only with the Podhaler device. The spray-dried powder also contains 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), calcium chloride, and sulfuric acid (for pH adjustment). The recommended dose is inhalation of four capsules twice-daily for 28 days, followed by 28 days of no tobramycin treatment and then a further 28 days of tobramycin therapy. Treatment duration greater than 3 cycles has not been evaluated [4]. The TOBI® Podhaler delivers 102 mg of tobramycin from the mouthpiece (4 capsules per dose) under standardized *in vitro* testing at a fixed flow rate of 60 L/min and volume of 2 L for 2 seconds.

The safety and efficacy of TOBI® Podhaler was established in a Phase III randomized, three-cycle, two-arm trial involving 95 cystic fibrosis patients between 6 and 21 years of age (mean age around 13 years) [1-3]. All patients had tested positive for P. aeruginosa. The participants were randomly assigned to receive TOBI Podhaler or a placebo for the first 28 days of the study. They then all received treatment with TOBI Podhaler for the rest of the trial. The results of the trial showed that patients treated with TOBI® Podhaler had a statistically significant increase of 12.5 percent in FEV1 compared to 0.09 percent in patients treated with placebo. The results were supported by data from other studies involving 487 patients.

TOBI® Podhaler is already approved in the European Union, Canada, Switzerland and other markets. It is expected to be available in the US in the second quarter of 2013 [4].

Karbinal™ ER (Tris Pharma Inc)

Five days later on 28 March 2013 the FDA approved Tris Pharma Inc's Karbinal™ ER, an extended release oral suspension containing 4 mg/ml of the anti-histamine, carbinoxamine maleate, for the symptomatic treatment of number of conditions including seasonal and perennial allergic rhinitis, vasomotor rhinitis and allergic conjunctivitis due to inhalant allergens and foods [5, 6]. It can be administered to adults and children of 2 years and older. The dose for adults and children of 12 years and above is 7.5 to 20 ml twice daily.

Karbinal ER is based on Tris Pharma's OralXR+™ technology [6, 7]. This technology involves complexing the drug with an ion-exchange resin to form drug-resin particles. In the case of carbinoxamine maleate, the ion-exchange resin chosen is sodium polystyrene sulfonate. Depending on the drug and the exact release characteristics required, at least a portion of these complexes are coated with a barrier coat of the water-insoluble polymer, polyvinyl acetate. Different release profiles can be obtained by mixing different proportions of the coated and uncoated drug-resin complexes, varying the thickness of the barrier coat and by addition of a release retardant, typically polyvinyl acetate, to the uncoated particles prior to coating.

Approval was based on the previous extensive clinical database on carbinoxamine maleate plus the results of single dose and multiple dose pharmacokinetic studies which showed that Karbinal ER at a dose of 16 mg per day was bioequivalent to the reference carbinoxamine immediate-release oral solution. Food had no effect on the pharmacokinetics of this product [5].

It is thought that approval of this product will give more choice to physicians, patients and parents as at present the only US approved preparations of carbinoxamine are immediate release with a four times-a-day dosing schedule [6].

References and Further Information

1. FDA approves TOBI Podhaler to treat a type of bacterial lung infection in cystic fibrosis patients
   http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345123.htm (Accessed on 31 May 2013)

2. Entry for TOBI Podhaler of Drugs@FDA
   http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/201688s000lbl.pdf (Accessed on 31 May 2013)

3. FDA approves Novartis TOBI® Podhaler™ for certain cystic fibrosis patients, the first and only dry powder inhaled antibacterial in US
   http://www.pharma.us.novartis.com/newsroom/pressreleases/137175.shtml (Accessed on 31 May 2013)

4. TOBI Podhaler website
   http://www.tobipodhaler.com/index.jsp (Accessed on 31 May 2013)

5. Entry on Karbinal ER on Drugs@FDA
   http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022556s000lbl.pdf (Accessed on 31 May 2013)

6. FDA Approves Tris Pharma's New Drug Application for Karbinal™ ER (carbinoxamine maleate) Extended-release Oral Suspension
   http://www.trispharma.com/news_karbinal_apr2013.php (Accessed on 31 May 2013)

7. Tris Pharma Inc US Patent Application 20130136797

DRUG DELIVERY COMPANIES

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Provided by Jeffry Grunkemeyer

ACTIVAERO (Gemuenden/Wohra, Germany)

Activaero is a privately held respiratory area specialist founded in 1998. Using its proprietary FAVORITE inhalation approach the company develops novel, significantly safer and more efficacious therapeutics for the treatment of severe lung diseases including asthma, Cystic Fibrosis, COPD and Pulmonary Hypertension. The company's development pipeline consists of partnered programs (co-developed with other pharma and biotech companies) and proprietary products (in-house development programs). In 2012, Activaero had one Phase III and two Phase II proprietary programs in development.

Fact sheet:

Founded:	1998
Location:	Gemuenden/Wohra, Germany (close to Frankfurt/Main)
Ownership:	Private
Employees:	40
Key technology:	**Favorite** Flow & volume controlled inhalation is a proprietary inhalation approach developed by Activaero. It enables exceptionally efficient drug deposition across the entire lung and past obstructions into the small airways. This region is typically not accessible for conventional nebulizer systems. FAVORITE therewith leverages the full therapeutic potential of respiratory medicines, helps spare drug and consequently maximizes efficacy without the side effects normally observed.
Products:	FLAVORESTIN – a drug-device combination therapy to wean severe oral corticosteroid dependent asthmatics off their oral steroids SCIPE – a drug device combination therapy to treat children with asthma
Development status	Finished pivotal clinical trial. Submission planned for end of 2013.
Partnerships:	Grifols, Ablynx, and others not disclosed
Website:	http://www.activaero.de
Contact:	Christian Pangratz, Chief Business Officer Robert-Koch-Allee 29 D-82131 Gauting, Germany Phone: +49 (0)89 897969-65 Fax: +49 (0)89 897969-12 E-Mail: christian.pangratz@activaero.de

DRUG DELIVERY PEOPLE

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Provided by Prof. Dr. Karsten Mäder

ABRAHAM (AVI) J. DOMB is a Professor for Medicinal Chemistry and Biopolymers at the Faculty of Medicine of the Hebrew University of Jerusalem. He earned Bachelors degrees in Chemistry, Pharmaceutics and Law studies and a PhD degree in Chemistry from The Hebrew University in Jerusalem, Israel. He did his postdoctoral training in the group of Bob Langer at MIT and Harvard Univ. Cambridge, USA. In the following years from 1988 to 1991 he joined the industry as R&D manager at Nova Pharm. Co., Baltimore, US. He has been a faculty member at the Hebrew University since 1991 and full Professor there since 1999. During 2007-2012 he headed the Division of Forensic Science at the Israel Police. His current areas of interest include biopolymers, drug delivery systems, bioactive polymers and forensic sciences.

Avi Domb combines academic research with the successful translation from academia to the clinical use. He has published around 350 papers in international leading journals. Over 150 patents are connected with his name, many of which have been incorporated in large-scale commercial applications: Gliadel® brain tumor implant (Guilford, U.S.); Superfloc® poly (hydroxamic acid) for purification of aluminum and cleaning swimming pools (American Cyanamid, U.S.); Deximmune™, cyclosporine capsule for treating transplant rejection (Dexxon, Israel); MAZE Water Maker™ - home/office water purification system (Strauss-Water, Israel); Canker Cover™ - adhesive patch for treating oral canker sore (Quantum, USA); Oramoist™ - adhesive patch for treating dry mouth (Quantum, USA); OrthoPass™ - CE mark for a biodegradable balloon installed between tissues for irradiation protection (Bioprotect & Orthospace, Israel); I-ABNTM - Rout Cannal Sealer with Insoluble AntiBacterial Nanoparticles (BJM, Israel).

ACADEMIC GROUPS: LIPOSOME TECHNOLOGY

This article gives a brief overview of academic groups based at European Universities working on liposome technology research. This is another publication in the 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 flavor of the groups involved. As it is a living document, our readers are most welcome to suggest other liposome research teams they are aware of for inclusion in our next edition (kromp@lipoid.com).

Ankara

Institution	Turkey, Ankara: Hacettepe University
Group	Faculty of Pharmacy / Department of Radiopharmacy
Key contact	Prof. Dr. A. Yekta Özer
Website	http://www.pharmacy.hacettepe.edu.tr/index.php?option=com_content&view=article&id=44%3Aradyofarmasi-anabilim-dal&catid=19&Itemid=10
E-Mail	ayozer@hacettepe.edu.tr
Research areas	- Tablet technology - Drug delivery systems - Radiolabeling and radioactive drugs

Basel

Institution	Switzerland, Basel: University Basel
Group	Pharmaceutical Technology
Key contact	Prof. Dr. Jörg Huwyler
Website	http://pharma.unibas.ch/research-groups/details/home/group/pharmaceuticaltechnology/
E-Mail	joerg.huwyler@unibas.ch
Research areas	- Biologicals - Drug Targeting - Nano-sized drug carriers

Birmingham

Institution	United Kingdom, Birmingham: Aston University
Group	School of Life and Health Sciences / Aston Pharmacy School
Key contact	Prof. Yvonne Perrie
Website	http://www1.aston.ac.uk/lhs/research/health/pharmacy/
E-Mail	y.perrie@aston.ac.uk
Research areas	- Formulation Engineering of Vaccines - Enhancing solubility and delivery of bioactive molecules using colloid science and technology - Delivery of drugs, vaccines and gene therapies using liposomes, niosomes and other novel particulate systems - Tissue engineering and regenerative medicine

Braunschweig

Institution	Germany, Braunschweig: Technical University Braunschweig
Group	Institute for Pharmaceutical Technology / Department of Pharmaceutics
Key contact	Prof. Dr. Christel Müller-Goymann
Website	https://www.tu-braunschweig.de/pharmtech
E-Mail	c.mueller-goymann@tu-braunschweig.de
Research areas	- Colloidal drug delivery systems (liposomes, nanoparticles, micelles) - Influence of drug delivery systems on human stratum corneum or cell constructs

Brno

Institution	Czech Republic, Brno: Czechoslovak Academy of Agricultural Sciences
Group	Veterinary Research Institute / Pharmacology and Immunotherapy
Key contact	Dr. Jaroslav Turanek
Website	http://www.vri.cz/en/institute
E-Mail	turanek@vri.cz
Research areas	- Nanoliposomes for development of recombinant vaccines and targetted immunotherapeutics - Toxic properties of nanoparticles - Synthetic multiepitopic vaccine agains borreliosis intended for veterinary applications

Brussels

Institution	Belgium, Brussels: University Libre de Bruxelles
Group	Laboratory of Pharmaceutics and Biopharmaceutics
Key contact	Prof. Karim Amighi
Website	http://www.ulb.ac.be/rech/inventaire/unites/ULB396.html
E-Mail	kamighi@ulb.ac.be
Research areas	- Creating new pharmaceutical forms - Improving manufacturing processes - Increasing the bioavailability of active molecules

Budapest

Institution	Hungary, Budapest: Semmelweis University
Group	Nanomedicine Research and Education Center
Key contact	Prof. János Szebeni
Website	http://kortan.sote.hu/
E-Mail	jszebeni2@gmail.com
Research areas	- Nanomedicine, biomedical application of liposomes - Immunology, artificial blood - Complement research

Cagliari

Institution	Italy, Cagliari: University of Cagliari
Group	Department of Environmental and Life Science
Key contact	Prof. Anna Maria Fadda
Website	http://www2.unica.it/dfct/index.php
E-Mail	mfadda@unica.it
Research areas	- Nanoparticular drug delivery systems - Properties and aggregation of amphiphilic molecules in aqueous environment - Dermal and transdermal drug targeting / Colon targeting - Hydrogels as delivery systems - Biopharmaceutical properties of solid dosage forms

Florence

Institution	Italy, Florence: University of Florence
Group	Department of Chemistry and Center for Colloid and Surface Science
Key contact	Dr. Sandra Ristori
Website	http://www.unifi.it/dipchimica/changelang-eng.html
E-Mail	ristori@unifi.it
Research areas	- Nano-structured systems as carriers for compounds of biomedical interest - Nano-structured systems as model matrices for the confinement of oscillating reactions

Freiburg

Institution	Germany, Freiburg: Albert-Ludwigs-University
Group	Department of Pharmaceutical Technology and Biopharmaceutics
Key contact	Prof. Dr. Rolf Schubert
Website	http://www.pharmtech.uni-freiburg.de/
E-Mail	rolf.schubert@pharmazie.uni-freiburg.de
Research areas	- Manufacturing and analysis of liposomes - Liposomal model membranes - New therapies with nanocarriers - Drug transport trough intestinal membranes

Freiburg

Institution	Germany, Freiburg: Albert-Ludwigs-University
Group	Department of Pharmaceutical Technology and Biopharmacy
Key contact	Prof. Dr. Regine Süss
Website	http://www.pharmtech.uni-freiburg.de/
E-Mail	regine.suess@pharmazie.uni-freiburg.de
Research areas	- Manufacturing and analysis of liposomes - Liposomal model membranes - New therapies with nanocarriers - Drug transport trough intestinal membranes

Groningen

Institution	The Netherlands, Groningen: University of Groningen
Group	University Medical Center Groningen / Department of Pathology and Medical Biology
Key contact	Dr. Jan Kamps
Website	http://www.rug.nl/research/pathology/medbiol/research/ec/ec_intro
E-Mail	j.a.a.m.kamps@med.umcg.nl
Research areas	- Endothelial targeted drug delivery - Development of targeted liposomal delivery systems for improved siRNA delivery - Endothelial cell dysfunction in disease

Heidelberg

Institution	Germany, Heidelberg: University Heidelberg
Group	Department of Pharmacy and Molekular Biotechnology / Pharmaceutical Technology and Biopharmaceutics
Key contact	Prof. Dr. Gert Fricker
Website	http://www.ipmb.uni-heidelberg.de/phazt/
E-Mail	gert.fricker@uni-hd.de
Research areas	- Drug transport across the blood-brain-barrier - Cellular transport systems - Drug targeting - Improvement of drug absorption from the gastro-intestinal tract

Jena

Institution	Germany, Jena: Friedrich-Schiller-University
Group	Department of Pharmaceutical Technology
Key contact	Prof. Dr. Alfred Fahr
Website	http://www.uni-jena.de/ls_fahr.html
E-Mail	Alfred.Fahr@uni-jena.de
Research areas	- Optimization of gene transfection into cells by liposomes - Topical application of liposomes as drug carriers - Therapy of cancer and arthritis by use of liposomes

Jerusalem

Institution	Israel, Jerusalem: Hebrew University-Hadassah Medical School
Group	Laboratory of Membrane and Liposome Research
Key contact	Prof. Chezy Barenholz
Website	https://medicine.ekmd.huji.ac.il/En/Publications/ResearchersPages/pages/chezyb.aspx
E-Mail	chezyb@ekmd.huji.ac.il
Research areas	- Biochemistry and biophysics of lipids and membranes - Amphiphile-based drug carriers, especially liposomes

Leiden

Institution	The Netherlands, Leiden: University Leiden
Group	Leiden/Amsterdam Center for Drug Research / Drug Delivery Technology
Key contact	Prof. Dr. Joke Bouwstra
Website	http://drugdeliverytechnology.leidenuniv.nl/
E-Mail	bouwstra@lacdr.leidenuniv.nl
Research areas	- Skin research - Transdermal and dermal drug delivery

London

Institution	United Kingdom, London: University College London
Group	UCL School of Pharmacy / Centre for Drug Delivery Research
Key contact	Prof. Kostas Kostarelos
Website	http://www.ucl.ac.uk/pharmacy/people/Pharmaceutics/pharmaceutics_rc/CDDR
E-Mail	k.kostarelos@ucl.ac.uk
Research areas	- Development of advanced delivery systems - Engineering of nanosystems

Munich

Institution	Germany, Munich: Ludwig-Maximilians University
Group	University Hospital of Munich / Department of Internal Medicine III
Key contact	PD Dr. Lars H. Lindner
Website	http://www.klinikum.uni-muenchen.de/Medizinische-Klinik-und-Poliklinik-III/de/forschung/liposom_kkg_hyperthermie/index.html
E-Mail	Lars.Lindner@med.uni-muenchen.de
Research areas	- Development and in vivo testing of thermosensitive liposomes for cancer therapy

Odense

Institution	Denmark, Odense: University of Southern Denmark
Group	Medicinal chemistry and Pharmaceutical Technology / Drug transport and Delivery
Key contact	Prof. Martin Brandl
Website	http://www.sdu.dk/en/Om_SDU/Institutter_centre/fysik_kemi_og_farmaci/Forskning/Forskningsgrupper/DrugTransportAndDelivery
E-Mail	mmb@sdu.dk
Research areas	- Optimization of drug transport - Improvement of drug absorption - Artificial liposomal membranes

Rotterdam

Institution	The Netherlands, Rotterdam: Erasmus University Rotterdam
Group	Erasmus Medical Center / Department of Surgery
Key contact	Dr. Gerben A. Koning
Website	http://surgical-oncology.nl/
E-Mail	g.koning@erasmusmc.nl
Research areas	- Loco-regional solid tumor therapy - Manipulation of the tumorpathophysiology in solid tumor therapy - Drug delivery: targeting, nanotools and hyperthermia - Receptor targeted radiotherapy

Tromsø

Institution	Norge, Tromsø: University of Tromsø
Group	Department of Pharmacy / Drug Transport and Delivery
Key contact	Prof. Natasa Skalko-Basnet
Website	http://en.uit.no/ansatte/organisasjon/hjem?p_menu=42374&p_dimension_id=96234
E-Mail	natasa.skalko-basnet@uit.no
Research areas	- Liposomes as novel drug delivery system in topical application - Biohydrogels - Topical formulations containing natural origin substances

Utrecht

Institution	The Netherlands, Utrecht: University Utrecht
Group	Department of Pharmaceutical Sciences / Biopharmacy and Pharmaceutical Technology
Key contact	Prof. Dr. Gert Storm
Website	http://www.uu.nl/faculty/science/EN/organisation/depts/pharmaceuticalsciences/research/pharmaceutics/Pages/default.aspx
E-Mail	G.Storm@uu.nl
Research areas	- Bio- and nanotechnology approaches to drug delivery - Targeting Inflammation to fight cancer - Immunogenicity of pharmaceutical proteins

Vienna

Institution	Austria, Vienna: University of Vienna
Group	Department of Pharmaceutical Technology and Biopharmaceutics
Key contact	Prof. Dr. Claudia Valenta
Website	http://www.univie.ac.at/pharm-technologie/valenta.html
E-Mail	claudia.valenta@univie.ac.at
Research areas	- Improvement of penetration and permeation of drugs through skin - Developing and testing of polymers and modified polymers as matrix for drug Topical delivery systems - Liposomes, nanoemulsions, microemulsions, cubic phases

Wroclaw

Institution	Poland, Wroclaw: University of Wroclaw
Group	Faculty of Biotechnology / Laboratory of Lipids and Liposomes
Key contact	Prof. Arkadiusz Kozubek
Website	http://www.ibmb.uni.wroc.pl/ak_gb.htm
E-Mail	kozubek@ibmb.uni.wroc.pl
Research areas	- Liposomes as drug carriers - Resorcinolic lipids

Wroclaw

Institution	Poland, Wroclaw: University of Wroclaw
Group	Institute of Biochemistry and Molecular Biology / Department of Genetic Biochemistry
Key contact	Prof. Aleksander F. Sikorski
Website	http://www.ibmb.uni.wroc.pl/afs.htm
E-Mail	afsbc@ibmb.uni.wroc.pl
Research areas	- Liposomes as carriers of boactive substances - Structure and function of membrane skeleton

Zurich

Institution	Switzerland, Zurich: ETH Zurich
Group	Institute of Pharmaceutical Sciences / Drug Formulation and Delivery
Key contact	Prof. Dr. Jean-Christophe Leroux
Website	http://www.galenik.ethz.ch/
E-Mail	jean-christophe.leroux@pharma.ethz.ch
Research areas	- Design of polyion complex micelles for antisense oligonucleotides and SiRNA delivery - Novel strategies for the treatment of celiac disease - Functionalized amphiphilic biodegradable polymers for drug targeting applications - Colloidal vesicles for the treatment of drug overdose

FEATURED ARTICLE

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Drug Delivery Systems Used To Deliver Opioids in Chronic Pain Therapy

Part III: Parenteral Depot Systems

By Johannes Bartholomäus, Burghöhenweg 5, 52080 Aachen

3. Parenteral depot formulations and devices

Technical solutions by drug delivery systems

This article is the third in a series dealing with drug delivery systems used to deliver opioids in chronic pain therapy. The first of these articles appeared in Issue 1/2011 of the Newsletter and covered oral prolonged release systems; the second in Issue 3/2012 dealt with transdermal systems. Oral formulations have a maximum dosing interval of about once daily and transdermal application allows for about up to once weekly administration. However, as chronic pain can last for months and years, it would therefore be advantageous to increase dosing intervals further in the direction of month(s). Such time intervals for controlled release of drugs require depot systems or devices that are implanted (and which probably must also be explanted after release) or in best case be manufactured from biodegradable polymers that can be injected. The depots would have to carry a large amount of a potent opioid drug and need to be extremely safe to avoid dose dumping and high initial bursts because of the adverse effects of opioid agonists e.g. respiratory depression that could become life threatening. Thus, only a very few development projects were started in this field. One of these approaches was the Chronogesic® system (Fig. 1) developed by Durect, a 1998 spin-off out of ALZA, based on the DUROS® technology.

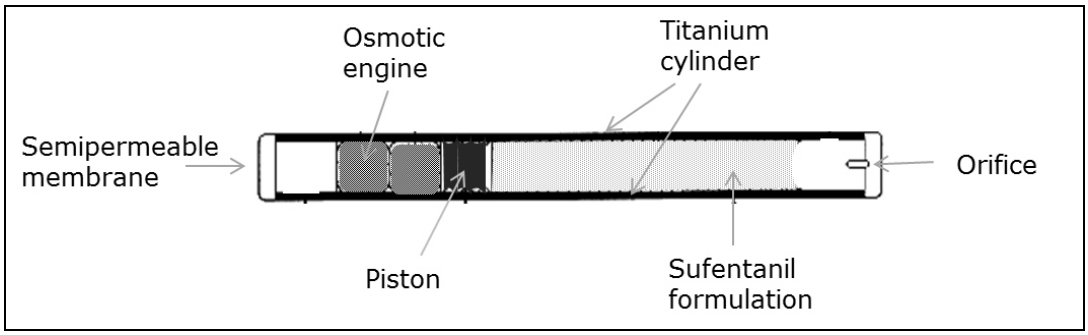

Fig. 1 DUROS® for sufentanil

DUROS is a miniature drug-dispensing pump made of a small titanium cylinder of about 4 mm in diameter and 4 cm in length driven by osmotic forces. At one end the cylinder is capped with a semipermeable membrane that controls the selective permeation of water into the system including zero-order penetration. Next to this control membrane is placed a kind of tablet consisting of osmotically active material. It swells and/or dissolves by means of the incoming water and generates the force to drive a piston at a controlled rate expelling the solution of the active ingredient placed between the piston and the very small orifice at the other end of the cylinder. In case of Chronogesic® sufentanil was chosen because it is an extremely potent opioid allowing for 3 months' dosing from the small 155 µl volume with a zero order release of 20–25 µg/h of active. In a dry environment e.g., during storage, no drug is released. After contact with an aqueous environment e.g., following subcutaneous implantation or in an in-vitro dissolution vessel, release starts after a lag-time of about a few days. This, compared to the duration of therapy, short lag time is part of the safety concept of the product as it avoids high initial bursts that may be found e.g. if the system is completely filled at room temperature to the very end into the orifice and thermal expansion of the filling volume occurs as the implant approaches body temperature after implantation. The in-vitro release of the system is shown in Fig. 2.

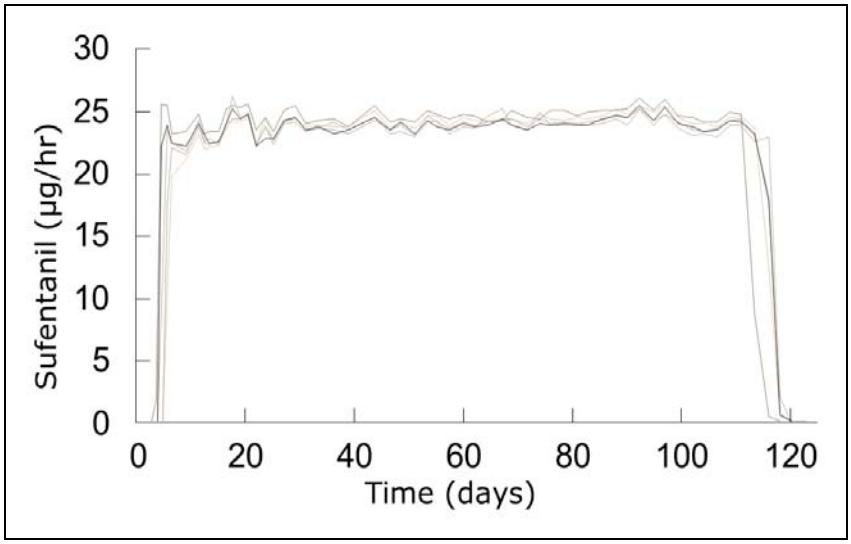

Fig. 2 In-vitro release of sufentanil from a DUROS®

Chronogesic® was licensed in the beginning of the 2000s by Durect to a partner to perform full clinical development, NDA submission and later marketing. Phase I and II studies showed that the principle worked *in-vivo*. However, the development was ceased after some years and the partner returned the rights to Durect.

In the field of chronic pain treatment with opioids practically no other particular development projects have been reported. Whereas for some other indications parenteral depot formulations have been developed and marketed or are under development. DepoDur®, a liposomal morphine depot based on phospholipids for epidural injection, was developed and marketed in the US and Europe for some years between the mid to end of the 2000s for the treatment of postoperative pain following major surgery. It was designed for 48 hour pain control by one single injection.

Another field in that opioid depot formulations have been developed is substitution therapy for opioid addicts. Besides oral solutions of methadone, sublingual tablets and orally dissolving films of high dose buprenorphine are already used for this indication. Titan Pharmaceuticals has developed a subdermal implant based on an ethylene-vinyl acetate (EVA) matrix for a 6 months' controlled release of buprenorphine that recently got a complete response letter from the FDA. The system offers the advantage that for a rather long period no daily administration and check that administration has occurred is necessary and there is reasonable assurance that the right amount of drug is being given in the intended way. At the end of the 6 month period the system has to be explanted and may be replaced by a new implant. A biodegradable system based on a controlled release matrix of fluid crystals is under development by Camurus and has been demonstrated to work in a Phase I/II trial. While its administration by injection with a small size needle without the need of explantation at the end of release could form an advantage over the formerly described EVA system, the dosing frequency is higher (between one week and one month).

Finally the opioid antagonist naltrexone was developed and is marketed by Alkermes in form of a biodegradable once per month depot based on polylactide-co-glycolide (75:25) microspheres. Vivitrol® was initially (2006) indicated for treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with Vivitrol®. It was later (2010) also approved for prevention of relapse to opioid dependence following opioid detoxification.

From Technical Solutions to Commercial and Environmental Factors and back

After oral prolonged release formulations of opioids had pioneered the commercial success of analgesics in treatment of chronic pain with up to once daily administration and transdermal patches with twice or once weekly administration

were commercially successful, too, it seemed to be the next logical step to add therapeutic options which would allow for even longer dosing intervals. However, this process appears to be impeded. Even if the technical challenges of avoiding initial bursts and achieving constant release rates over months were overcome, none of the products in the indication chronic pain made it to the market or even reached the registration stage. One reason may the challenge of achieving very narrow and constant release rates required in the treatment of pain; whereas, in the field of substitution therapy with e.g., buprenorphine, the therapeutic limits for serum concentrations may be wider since buprenorphine is often described as a partial opioid agonist and the addicts treated are often tolerant to high opioid doses. Another reason may be that chronic pain although it is called "chronic" is not "constant" over time. Thus, there may be a need for dose adjustments within less than one or three month treatment periods. From this point of view drug delivery systems with constant release rates seem to have reached the limit of their usability for the treatment of this indication and developers will have to break through new, but yet not defined frontiers to achieve progress in the field.

However, by using medical devices to control the delivery of drugs, there are solutions to cope with flexible adjustments of doses during long term treatment with opioids. For example, patients with moderate to severe pain lasting more than 6 months, patients who are impaired in their daily life by pain or who cannot be treated sufficiently by other therapy are indicated for implantation of a drug pump like the SynchroMed® II pump. In treatment of pain such a pump is implanted into a subcutaneous pocket often in the lower abdomen and releases the drug solution intrathecally into the spinal column via a catheter. The typical opioid used in this therapy is morphine in form of an aqueous isotonic solution. Compared to oral or intravenous administration the equivalent dose of morphine via intrathecal application is said to be 300 times (oral) and 100 times (iv) lower, respectively. Thus, 20 mg morphine administered by a medical pump intrathecally may replace 2 g iv or 6 g of oral morphine. The pumping rate of the system can be tailored individually to the needs of the patient by the physician and can also be adjusted by remote control at later time points according to changing needs of the patient. Beside constant pumping rates profiles, different rates over the day and bolus pulses are possible, too. Moreover, in cases where the patient needs more drug to cope with unexpected episodes of pain or pain peaks, pre-defined morphine boli can be self-administered via a personal remote control.

Given the above example it would appear that the right combination of a medical devices and a suitable formulation could be the solution to patients' problems with chronic pain. Since patients' needs should always be the basis for the design of a drug delivery solution, this approach might be one of the future directions of drug delivery.

As already indicated in the paragraph on medical pumps, pain is not always constant and breakthrough pain episodes often occur in chronic pain even if it is being treated by long term release opioids. Thus, specific formulations able to rapidly administer analgesics into the bloodstream may add to the overall quality of pain treatment and will be described in the last part of this series.

This featured article is Part 3 of a series that will be finalized in one of the next issues of the Drug Delivery Newsletters.

DRUG DELIVERY LITERATURE

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Provided by Dr. Carsten Timpe

RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY

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ABOUT THE FOCUS GROUP

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The APV Drug Delivery Focus Group (APV DD) is a section of the APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik e.V. / International Association for Pharmaceutical Technology), a major European society for those sharing a professional interest in pharmaceutical sciences. The Focus Group was established in 2003 in response to the increasing importance of drug delivery within modern pharmaceutics.

Read more. ***Contact us.***

COMBINING SCIENCE AND TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

OUR MISSION STATEMENT:

Modern drug delivery research and development is a truly multidisciplinary approach and must combine all relevant scientific, technical, medical and regulatory aspects required for the design, preparation, testing, manufacturing and registration of drug delivery systems and their components. It is the mission of the APV Drug Delivery Working Group to foster and promote all aspects of research and development required to transform drug molecules into safe, applicable and acceptable drug delivery systems, which provide therapeutic benefit, convenience to the patient and improve patient compliance.

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

All disciplines relevant to the above mentioned areas of drug delivery R&D are invited to contribute to the APV Drug Delivery Group:

Pharmaceutics, Biopharmaceutics, Analytics, Biology, Physical Chemistry, Biochemistry, Physics, Engineering Sciences, Nano Technology, Material Sciences, Polymer Science, Toxicology, Drug Safety, Clinical Research, Drug Regulatory Affairs, etc.

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