APV FOCUS GROUP DRUG DELIVERY

COMBINING SCIENCE & TECHNOLOGY TO CREATE ADVANCED DRUG DELIVERY SYSTEMS

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER **ISSUE 3/2011**

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DRUG DELIVERY EVENTS

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Provided by Christoph Blümer

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

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

Chairs: Dr. Joachim Herrmann, Dr. Willmar Schwabe GmbH & Co KG, Karlsruhe, Germany
Prof. Dr. Johannes Bartholomäus, Pharmakreativ Consulting, Aachen, 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/costumer 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

Nanocarriers for drug delivery (APV Course 6409)

November 17-18, 2011, Berlin, Germany

Chairs: Prof. Dr. Karsten Mäder, Martin Luther University Halle/Saale, Germany
Dr. Carsten Olbricht, Bayer Schering Pharma AG, Berlin, Germany

It is the aim of the workshop to provide an overview of different types of nanocarrier and to discuss what they do and do not share in common. Well known scientists from industry and academia will provide detailed information on the physicochemical properties and the biofate of liposomes, polymer nanoparticles, nanosized liquid crystals, solid lipid nanoparticles, nanoemulsions, nanostructured lipid carriers, nanosuspensions, water soluble polymer conjugates, polymer micelles and nanodiagnostics. The challenges the Pharma Industry face in developing nanocarriers will also be covered. The workshop will enable the participants to identify critical aspects of nanocarriers and to evaluate, select and improve the carrier, the material and the process in a rational, performance based way.

Details

Suggest a meeting to be announced!

Buccolam® (ViroPharma)

On 6 Sept 2011 ViroPharma announced that the European Commission had granted a Centralized Paediatric Use Marketing Authorization (PUMA) for Buccolam® (midazolam, oromucosal solution) [1]. This medication is indicated for treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents, from 3 months to less than 18 years of age. This action follows the product receiving a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency in June [2]. This approval is the very first granted through the centralised PUMA procedure which is for medicinal products exclusively for paediatric use. The procedure was designed to encourage companies to conduct paediatric development on previously authorised medicines that are no longer subject of a supplementary protection certificate (SPC) or a patent qualifying for a SPC [3].

Buccolam is a pre-measured, age-specific dose formulation for buccal administration. It is supplied as prefilled syringes containing 2.5 mg drug. Approval was based on the results of five clinical trials in a total of 688 children [4]. In four of these studies the buccal formulation was compared to rectally administered diazepam, the current standard treatment. The results of these studies show that Buccolam is either comparable or superior, in terms of both effectiveness and speed of onset of action, to the present therapy. In addition, its administration via the buccal route is far more convenient and less distressing for both patient and carer alike [1, 4].

The approval triggers an additional payment of £10 million sterling to the former owners of Auralis Limited [1], the company which originally developed the product and which was acquired by ViroPharma in May2010 [5].

Nucynta® ER (Janssen Pharmaceuticals)

On 25 August 2011 the FDA approved Nucynta extended-release oral tablets C-II from Janssen Pharmaceuticals Inc [6]. The tablets contain the mu-opioid agonist, tapentadol, and are indicated for the treatment of moderate to severe chronic pain in adults where 24-hour pain relief is required for an extended period. They are available in 50 mg, 100 mg, 150 mg, 200 mg and 250 mg strengths and are for twice daily administration. The film-coated tablets contain polyethylene oxide, hypromellose, polyethylene glycol and alpha-tocopherol.

The efficacy of Nucynta ER was demonstrated in one randomized active and placebo controlled study in lower back pain (LBP) and one randomized placebo controlled trial in patients suffering from painful diabetic peripheral neuropathy (DPN). The studies showed that after 15 and 12 weeks respectively, patients receiving Nucynta ER in the LBP and DPN studies had significantly less pain than those taking placebo.

References and Further Information

[1] ViroPharma's Buccolam® (Midazolam, Oromucosal Solution) Granted European Marketing Authorization for Treatment of Acute Seizures
http://ir.viropharma.com/releasedetail.cfm?ReleaseID=603415 (Accessed on 30.9.2011)
[2] ViroPharma Announces Positive CHMP Opinion for Buccolam® (Midazolam, Oromucosal Solution) in the European Union
http://ir.viropharma.com/releasedetail.cfm?ReleaseID=587147 (Accessed on 30.9.2011)
[3] Questions and Answers on the Paediatric Use Marketing Authorisation (PUMA)
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/09/WC500112071.pdf
(Accessed on 30.9.2011)
[4] Buccolam: EPAR - Product Information on EMA website
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002267/human_med_001479.jsp&mid=WC0b01ac058001d124 (Accessed on 30.9.2011)
[5] Annual Report 2010 on ViroPharma website
http://ir.viropharma.com/annuals.cfm (Accessed on 30.9.2011)
[6] Entry on Nucynta ER on Drugs@FDA
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist (Accessed on 30.9.2011)

NANOTECHNOLOGY

The design, manufacture, characterisation, and application of structures, devices, and systems by controlled manipulation of size and shape at the atomic, molecular, and macromolecular level and nanometre scale, associated with at least one characteristic or property which is exclusively due to the nanoscale.
Write a comment on this definition

There is much debate on the proper definition of nanotechnology. Most definitions that the scientific community or organisations have come up with to date have included a size limit of below 100 nm, which is the scale at which

size-dependent quantum effects come to bear (see e.g. the definition by the US National Science Foundation (http://www.nsf.gov/crssprgm/nano/reports/omb_nifty50.jsp). Currently, however, there is a trend to challenge the 100 nm size limit as it excludes numerous materials and devices, especially in the pharmaceutical field. For example, a liposome whose surface is spiked with a defined number of targeting and/or cell penetration ligands would typically have a diameter of above 100 nm and, thus, not fall within the scope.

NANOMEDICINE

Nanotechnology applied to medicine. Write a comment on this definition

Nanomedicine includes various subcategories of nanotechnology, such as material science, molecular nanotechnology, bionanotechnology, interface and colloid science, nanosensors, and potentially also nanorobotics and nanoelectromechanics. An example of a nanocarrier useful in nanomedicine is a crosslinked micelle whose surface is modified with a cell-specific targeting moiety.

Suggest a term to be defined ***Suggest a definition***

DRUG DELIVERY COMPANIES

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Provided by Jeffry Grunkemeyer

SKYEPHARMA (London, UK)

SkyePharma is a specialist drug delivery company developing oral and inhalation products. With a wide range of patented and proven technologies, SkyePharma helps to make good drugs better.
We partner with a wide variety of companies from big Pharma, such as GlaxoSmithKline, Novartis, Sanofi-aventis, AstraZeneca and Roche to a range of smaller speciality pharmaceutical companies. SkyePharma's proprietary drug delivery technologies enable the development of new formulations of existing products as well as new chemical entities to provide a clinical benefit to patients.

Founded:	1996
Location:	Headquarters: London, UK R&D: Muttenz (Basel), Switzerland Manufacturing: Lyon, France
Ownership:	Public company, listed on the London Stock Exchange
Employees:	212
Key technology:	**Developing Oral and Inhalation Products** SkyePharma's Geomatrix™ and Geoclock™ technologies enable controlled- or timed-release versions of immediate-release products to be developed providing advantages to both partner companies and patients. The Group's inhalation technologies include formulation as well as device technologies and encompass metered dose inhalers and dry powder inhalers. With research and development facilities in Switzerland and manufacturing in France, SkyePharma offers a comprehensive range of services from feasibility through to commercial scale manufacture. **Oral Formulation Technologies**

FORMULATION CHALLENGE	SKYEPHARMA SOLUTION
Specific modified release pattern	Geomatrix
Time release / Chronotherapy	Geoclock
Multiple pulse profile	GeoPulse
Low bioavailability (BCS II and BCS IV)	Insoluble Drug Delivery (IDD). Dissocubes
Upper GIT delivery / absorption window	Gastro-Retentive Systems (OGRS)
First Pass Effect / rapid onset	Medicated Chewing Gum - GeoGum
Abuse deterrence (eg opioids, controlled substances)	Tamper resistant formulation

Inhalation Technologies

FORMULATION CHALLENGE	SKYEPHARMA SOLUTION
Robust and reproducible dosing	SkyePharma formulation and device technologies aim to achieve this
Long room temperature shelf life (≥ 2years)	SkyeProtect™ SkyeDry™, and SkyeStabe™ technologies
Moisture protection	SkyeProtect amd SkyeDry
Breath actuation vs. active drug dispersion	SkyeHaler™ DPI is breath actuated; MDI is active dispersion, which can be coupled to breath actuation, e.g. BAI
Flow rate independent dosing with breath actuated devices	SkyeHaler DPI achieves this via a threshold flow rate and medium resistance
Efficient lung deposition	SkyeFine™ when necessary
Target delivery to specific lung regions, e.g. deep lung deposition for systemic uptake	ISS-P™ nanotechnology

Products:

There are twelve products approved in the areas of oral, inhalation and topical delivery and additional products submitted for approval that incorporate the Group's proven proprietary technologies. The Group's products are marketed throughout the world by leading pharmaceutical companies.

Approved Products

LICENSEE/ PARTNER	PRODUCT NAME	GENERIC NAME	INDICATION	MARKETED
INHALATION				
AstraZeneca	Pulmicort® HFA-MDI	Budesonide	Asthma	yes
ORAL				
sanofi-aventis	Xatral® OD/ Uroxatral ®	Alfuzosin	BPH	yes
GlaxoSmithKline	Requip® Once-a-day	Ropinirole	Parkinson's disease	yes
GlaxoSmithKline	Paxil CR™	Paroxetine	Depression	yes
Sciele Pharma (Shionogi)	Triglide®	Fenofibrate	Lipid disorders	yes
Sciele Pharma (Shionogi)	Sular®	Nisoldipine	Hypertension	yes
Roche	Madopar DR®	Levodopa + Benserazide	Parkinson's disease	yes
Cornerstone Therapeutics	ZYFLO CR®	Zileuton	Asthma	yes
Therabel	Coruno®	Molsidomine	Angina	yes
Ratiopharm	diclofenac-ratiopharm® uno	Diclofenac	Pain/inflammation	yes
Horizon Europe	Lodotra®	Prednisone	Rheumatoid arthritis	yes
TOPICAL				
Nycomed/Almirall	Solaraze®	Diclofenac	Actinic keratosis	yes

Development status:	**Pipeline Products**

LICENSEE/ PARTNER	PRODUCT	ACTIVE	PRIMARY INDICATION	PH I	PH II	PH III
SkyePharma (US)	Flutiform™	Formoterol Fluticasone	Asthma	Complete	Complete	Complete
Mundipharma (Europe)	Flutiform™	Formoterol Fluticasone	Asthma	Complete	Complete	Complete
Kyorin (Japan)	Flutiform™	Formoterol Fluticasone	Asthma	Complete		
Horizon (US)	Lodotra®	Prednisone	Rheumatoid arthritis	Complete	Complete	
Somnus	SKP-1041	Zaleplon	Sleep maintenance	Complete	In progress	
Somnus	SKP-1052		Diabetes	2011		

Partnerships:	See above
Website:	http://www.skyepharma.com
Contact:	Yves Decadt, VP Business Development Eptingerstrasse 61 CH-4132 Muttenz Switzerland Office: +41 61 467 5531 Mobile: +41 78 655 3950 E-Mail : y.decadt@skyepharma.com

DRUG DELIVERY PEOPLE

Provided by Prof. Dr. Karsten Mäder

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DR. ANDREAS BRIEL studied chemistry at the Philipps University in Marburg (Germany) with the main focus on physical chemistry of polymers and subsequently developed research interests in the field of structure control of macromolecules with different nanoarchitectures. He completed his PhD studies in 1996 at the Max Planck Institute of Colloids and Interfaces (studying classical polyelectrolyte effects in polymer analytics).

In 1997 he joined Schering AG in Berlin and worked for 3 years on the pharmaceutical development of Ultrasound Contrast Agents (supporting Phase I & II clinical trials) and was international project team leader for novel contrast agents. Hereafter he spent 2 years in the Drug Delivery Systems department and 2 years in the CMC Technology Office of Schering, evaluating recent developments in drug delivery technologies. From 2004 to 2008, he was involved in Schering's Corporate Research Business Area "Diagnostic Imaging" and successfully established his own research team dealing with special research topics on nanomedicines.

As a founder and since June 2008 the Managing Director of *nanoPET Pharma* GmbH, Berlin, he is in charge of a Diagnostic Imaging company with currently 14 employees and 21 diagnostic imaging products marketed worldwide (www.viscover.com).

Andreas is a proven expert in Nanotechnology, *in vivo* Diagnostics and Drug Delivery Systems.

He is chairman of the *Association of Colloids and Interfaces Berlin/Brandenburg*, founded in 2001, and since 2003 he is also lecturer for "Novel Technologies and Innovation" at the University of Applied Sciences in Berlin. Additionally, he is involved in several initiatives as a consultant to the German government (e.g. BMBF-NanoforLife) and the European Commission (e.g. European Nanotechnology Platform on Nanomedicine) and the European Science Foundation (Forward Look on Nanomedicine) to define a common future vision regarding Nano(Bio)Medicine and the development of a strategic research agenda, which identifies research and innovation priorities to implement this vision at an European level.

This is the second issue of the recently established newsletter section, intended to give a brief tabulated overview on academic groups of European Universities working in a distinct drug delivery area. In this issue groups working on **PULMONARY DRUG DELIVERY** are presented.

Almost all internet websites of European universities offering the study of pharmacy have been evaluated for key words like e.g. respiratory, pulmonary, inhalation, inhaler, inhale, aerosol, nebulizer, nebulize and lung. Ten groups have been identified. The author would like to encourage all readers to feed back if a group is missing. This list is not intended to be comprehensive and it is a living document to be updated from time to time. Contact

Belgium, Brussels

Institution	Catholic University of Louvain (UCL – Brussels), Belgium.
Group	Pharmaceutical Technology Unit
Key contact	**Prof. Dr. Véronique Préat**
Website	http://www.uclouvain.be/en-farg.html
E-Mail	Veronique.Preat@uclouvain.be
Research areas	• Inhalation aerosols of biotech drugs. • Systemic absorption of peptides and proteins from the lung. • Design of dry powder aerosols with elevated deep lung deposition. • Excipient selection for pulmonary drug delivery; GRAS excipients with potential vaccine adjuvant properties. • Bioavailability of inhaled macromolecules in the lung. • Vaccine delivery to the lung and clearance by alveolar macrophages. • Optimization of immunization efficacy by designing dry powder aerosols with an appropriate deposition within the lung.

Germany, Bonn

Institution	Rheinische Friedrich-Wilhelms-Universität, Bonn, Germany.
Group	Fachgruppe Pharmazie / Pharmazeutische Technologie
Key contact	**Prof. Dr. Klaus-Jürgen Steffens**
Website	http://www.pharma.uni-bonn.de/www/pharmtech/forschung/steffens
E-Mail	steffens@uni-bonn.de
Research areas	• Aerosolization of liquids, nebulization, Laval nozzle. • Spray-dried powders for inhalation. • Particle disaggregation of spray-dried proteins • Surface modification of lactose for inhalation with $scCO_2$.

Germany, Kiel

Institution	Christian-Albrechts-Universität zu Kiel, Germany.
Group	Department of Pharmaceutics and Biopharmaceutics
Key contact	**Prof. Dr. Hartwig Steckel**
Website	http://www.uni-kiel.de/Pharmazie/technologie/eng/rf.htm
E-Mail	rmueller@pharmazie.uni-kiel.de
Research areas	• Pharmaceutical aerosols (DPI, MDI, powder rheology, particle sizing, nebulizers). • Dry powder inhalers (drug spheronisates, novel inhaler devices, novel formulation strategies for DPIs). • Metered-dose inhalers (precipitation in liquefied propellant, nanoparticles). • Aerosol particle sizing (impaction devices, laser diffraction, image analysis, novel optical aerosol particle size distribution measurement system). • Nebulizers (aqueous solutions and suspensions, cyclodextrin enabled solubilized systems, freeze drying of proteins and peptides, nano-supensions). • Nasal delivery (nasal powder formulations for NCE and NBE).

Germany, Marburg

Institution	Philipps–Universität Marburg, Germany.
Group	Institut für Pharmazeutische Technologie und Biopharmazie
Key contact	**Prof. Dr. Thomas Kissel**
Website	http://www.uni-marburg.de/fb16/iptb/forschung/akkissel/forschung
E-Mail	kissel@staff.uni-marburg.de
Research areas	• Inhalative depot formulations • Encapsulation, release and degradation of tailor-made bio-degradable polymers. • Stabilization and characterization of nano-supsensions. • Characterization of nanoparticles by dynamic light scattering, laser diffraction and cascade impaction (NGI). • Treatments with various types of nebulizers and DPIs. • Ex vivo research with isolated rabbit lungs.

Germany, Saarbrücken

Institution	Universität des Saarlandes, Saarbrücken, Germany
Group	Biopharmazie und Pharmazeutische Technologie
Key contact	**Prof. Dr. Claus-Michael Lehr**
Website	http://www.uni-saarland.de/de/campus/fakultaeten/professuren/ naturwissenschaftlich-technische-fakultaet-iii/pharmazie/professuren-fr-82-pharmazie/lehr/research.html
E-Mail	lehr@mx.uni-saarland.de
Research areas	• Biological barriers / respiratory tract. • NanoINHALE: cell culture based in vitro testing of the retarding effect and biocompatibility of extended release formulations in the lung; clearance of particles from the lung. • NanoCARE: adhesion, permeation and cell uptake of nanoparticles to lung cells. • Inhalable carrier systems for the cellular targeting of telomerase inhibitors.

United Kingdom, Cardiff

Institution	Cardiff University, United Kingdom.
Group	Pharmaceutical Technology
Key contact	**Prof. Glyn Taylor**
Website	http://www.cardiff.ac.uk/phrmy/contactsandpeople/fulltimeacademicstaff/taylor-glynnew.html
E-Mail	taylorg@cf.ac.uk
Research areas	• Pulmonary barriers to drug absorption. • Enhancing the systemic delivery of protein and peptide drugs using agents which alter the nature of the biological barrier to absorption. • Physical methods to produce aerosols optimised for specific regional deposition in the respiratory tract.

United Kingdom, Kent

Institution	Medway School of Pharmacy, Kent, United Kingdom.
Group	Chemistry and drug delivery
Key contact	**Prof Iain Cumming**
Website	http://www.msp.ac.uk/about/staff/iain-cumming.html
E-Mail	k.i.cumming@gre.ac.uk
Research areas	• Transdermal, controlled release, pulmonary and nanoparticle drug delivery systems and their application to pharmaceutical products.

United Kingdom, Liverpool

Institution	Liverpool John Moores University, United Kingdom.
Group	School of Pharmacy and Biomolecular Sciences / Drug Delivery and Material Sciences
Key contact	**Prof. James Ford**
Website	http://www.ljmu.ac.uk/PBS/research/drugdelivery/Index.htm
E-Mail	j.l.ford@ljmu.ac.uk
Research areas	• Bio and non-biodegradable polymeric porous materials as articles for aerosol delivery. • Models of upper airways to predict formulation performance. Inertial impaction techniques (ACI, MSLI, TSI). • Porous polymer formulations for aerosol delivery to the lungs.

United Kingdom, London

Institution	King's College London, United Kingdom.
Group	Drug Delivery Group Research
Key contact	**Professor Gary P. Martin**
Website	http://www.kcl.ac.uk/schools/biohealth/research/pharmsci/research/groups/delivery/
E-Mail	gary.martin@kcl.ac.uk
Research areas	• Novel strategies for drug delivery by inhalation and the treatment of respiratory disease. • Aerosol formulations from dry powder and pressurized inhaler devices. • Biopharmaceutics of particle-cell interaction, including gene therapy, and the characterization of bacteria in lung diseases such as cystic fibrosis. • Inhaled drug dosimetry, disposition, toxicity and pharmacokinetics.

Netherlands, Groningen

Institution	University of Groningen, Netherlands
Group	Department of Pharmaceutical Technology and Biopharmacy
Key contact	**Dr. Anne de Boer**
Website	http://www.rug.nl/fmns-research/pharmaceutical-technology-and-biopharmacy/research/inhalatieonderzoek
E-Mail	a.h.de.boer@rug.nl
Research areas	• Design and development of new dry powder inhalers (Novolizer, Twincer). • Formulation development for dry powder inhalers. • Aerosol characterization techniques. • Clinical research using dry powder inhalers.

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

FEATURED ARTICLE

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TTS MANUFACTURING TECHNOLOGY

By Michael Horstmann, PhD, tesa SE, Hamburg, Germany

1. Introduction

As manufacturing of transdermal products is not routine practice in pharmaceutical companies, introduction of manufacturing technology for this dosage form presents scientific and financial hurdles which can discourage firms from exploiting this route of delivery. However, these hurdles can be overcome by the selection of a suitable specialized and experienced partner for production.

This selection should ideally occur when the product is still at an early stage, as it is a key necessity to take into account process line requirements right at the start of the development of a new transdermal formulation. Aveva, Noven, LTS, Acino, Teikoku Seiyaku, Nitto and Hisamitsu are examples of established service providers of transdermal manufacturing, while others, such as Corium in the US or tesa's new pharma site in Hamburg, Germany, are newer entrants to this field.

Generally, there are nine standard process elements in transdermal manufacture which correspond to different production phases:

1. Processes for the API, its particle structure and its potential embedding in pre-processed coatings, complexes or aggregates
2. Processes to dissolve essential individual excipients like polymers
3. Manufacture of the coatable / spreadable mass(es), with or without API
4. Coating and drying
5. Lamination processes
6. Slitting
7. Converting
8. Primary packaging
9. Secondary packaging

Despite in later phases being continuous by design, transdermal processes are batch-driven as it is difficult to produce the spreadable mass containing the API in a homogenous, continuous fashion. If laminates with different drug-containing layers are used, it is common to define the layer with the highest drug content as batch-defining.

2. History

"Emplastra" were in a very simple sense the predecessors of transdermal therapeutic systems. They were first produced in ancient times (Egypt, Greece, Rome, and mediaeval times in Europe). Late in the 19th century, these traditional formulae were first "industrialized" by means of "drug in adhesive" continuous spreading and solidification processes. Between about 1890 and 1960, these products fell out of fashion and in consequence the underlying processes were also forgotten apart from a few exceptions.

Alza's re-invention of topical and systemic transdermal therapy began with a combination of a reservoir with a controlling membrane layer in a patch. This concept was considered both new (compared to previous systems) and simple (involved simple lamination processes). It dominated production and design technology between 1970 and 1990. Most systems during this period were produced by combining / laminating drug-free laminates of industrial adhesive layers (available as commodities) with foil-like membranes. Initially only liquid-containing, sealed reservoirs of the drug ingredient were generated e.g. in the case of Estraderm®, the first hormone patch. In other examples, the active ingredient was dissolved or dispersed in a layered reservoir structure which was quite often devoid of adequate adhesive characteristics. In all these processes, no large investments in coating and drying equipment were necessary and production lines could be kept simple and comparatively small. However, these patches had some disadvantages in terms of visual appearance and/or performance.

With the introduction of the first matrix (drug in adhesive) systems in the 1980s and 1990s (e.g. Nitro-Dur®, Deponit® for nitroglycerin, Systen®, Fem7®, Dermestril® for estradiol), systems became more flexible and consumer-friendly and, due to the omission of restricting membranes, drug utilization increased with reduced patch size. These technologies were in many cases initially created and honed in the hands of medical adhesive makers like Nitto, 3M, Beiersdorf and Lohmann. Skilled owners and operators of pre-existing industrial process lines for coating, drying and laminating on a large scale converted them into pharma lines. This process is still going on.

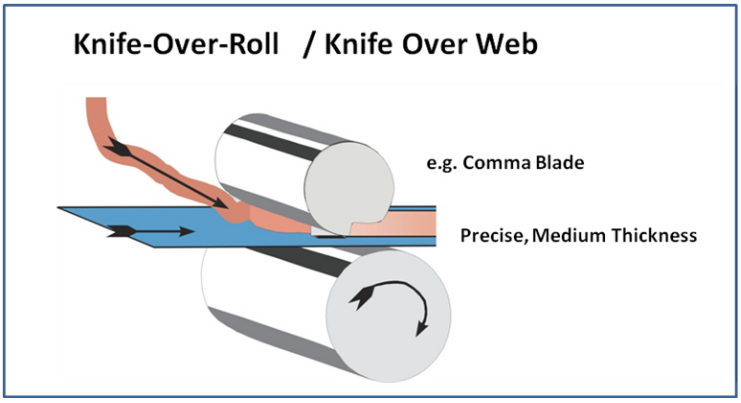
3. Established standard process sequence

According to "Quality by Design" principles, the formulation should get more rugged to the peculiarities and challenges of the process. However, in the case of transdermal formulations, innovative developers tend to add new risk factors (like the addition of volatile enhancers, phase borders, polymer blends and borderline saturation status of the API) rather than reduce them. This is the unique challenge of formulation in conjunction with process design and requires a high degree of interdisciplinary thinking. Most transdermal formulations contain the API in solution, a state in which it must reliably remain during the entire shelf life of the product. However, there have been cases where under certain storage conditions, re-crystallisation of the active ingredient occurred. This issue can be avoided by the performance of adequate solubility studies in the full knowledge that polymers tend to super-saturate any monomeric compound quite efficiently. Less known is the fact that re-crystallisation may even occur in the case of solid drug dispersions in the formulation. Like in ointments, there is a tendency for larger crystals to grow and smaller particles to shrink due to dissolution. The best and most sensible method to monitor for changes of this kind are *in-vitro* release profile tests.

Nowadays most polymers are available ready dissolved in organic solutions. Despite this it may be advisable for the drug delivery manufacturing companies to carry out polymer dissolution as this gives better process control and more flexibility in switching pharmacopoeial solvent quality. However, novices in this technology will be surprised as to the many mistakes that can be made which extend polymer dissolution time unnecessarily. In order to dissolve, for example, polyisobutylene (PIB) or synthetic rubber, it is first necessary to generate freshly calendered-flat sheets as these enable even access of solvent to the polymer during the dissolution process. Further processing has to be done in

a closed, explosion-proof environment, where high-shear kneading processes as well as solvent diffusion contribute to polymer dissolution. Care needs to be taken not to reduce the molecular weight of the polymer by mechanical force. After sometimes several days, a clear, isotropic solution of the polymer is achieved.

The main factors controlling content and content uniformity, besides the solids content in the homogenous coating mass, is the exactness of the caliper of the coating substrate, the choice of the coating process and the precision and selection of the tooling.



Numerous practical ways of spreading liquid or semi-solid masses on a web-like substrate are established. What most of them have in common is that a gap is formed between two rollers or a roller and a blade, which not only accomodates the adhesive, but also the substrate which thus adds to the caliper variability of the rollers. This is the reason why in general roll coaters may contribute rhythmic variabilities which follow sinusoidal curves of different frequency dependent on roller geometry, individual speed or even the caliper variability of the basis foil. For thin layers of less than 50 micrometres solid thickness, it is for physical reasons already difficult to obtain less than 5 % variability with roller coaters.

Coating process – the art of reproducible dosing

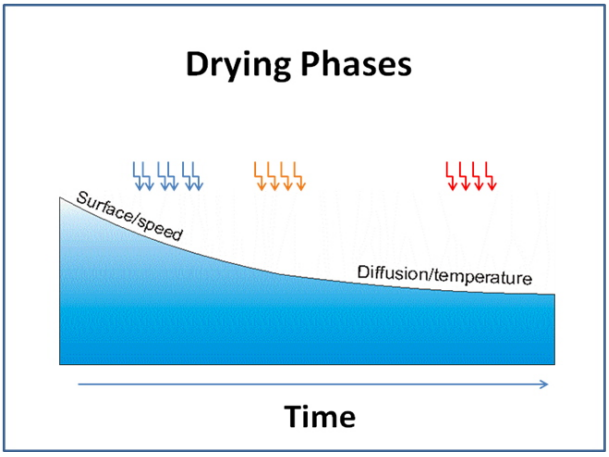
Independent of the proceeding information, current pharmaceutical coating processes for transdermals include:

- Roll or knife-over roll coating processes, where the gap between a roller and another roll / knife determines dosage accuracy. The support foil contributes to the imprecision by its own tolerability. There are no severe and unexpected contributions from machine speed variation.
- Extrusion processes. The coating mass is extruded through a flat die. The precision is mainly dictated by the constancy of the pumping system as well as the precision of the flat extrusion die over the width. As this extrusion process is independent of the line speed, a strict ratio needs to maintained and controlled. On the other hand, there is less dependence on substrate quality. The main application is hot melt extrusion.

Both general process methodologies have their value and are the basis of successful production processes for layers of about 30 to 100 micrometres with high precision and content uniformity.

Drying processes

Being connected to the dosing equipment, drying usually attracts less attention but it involves a larger share of the commercial effort and investment. Obviously, removal of process solvents is the main target, usually within the limits given by the ICH residual solvents guideline. Exceeding certain temperature limits may however lead to losses and excessive degradation. In real life, process developers need to compromise between acceptable volatile residues, acceptable losses and degradation.



The initial phase of drying involves lower temperatures at high speed; in later phases, diffusion of solvents within the matrix prevails as the process-time dictating phenomenon. In this later phase, the temperature is raised continuously based on experience and experimental trials in order to facilitate diffusion but avoid formation of bubbles.

Printing processes

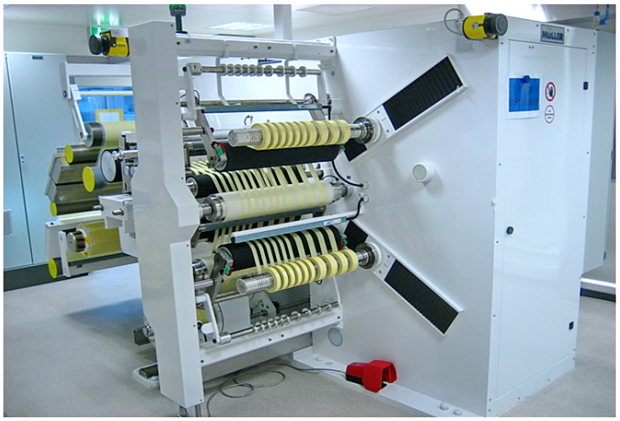
In case of volatile ingredients, specifically active ingredients, coating processes cannot ensure that all of the active ingredient is retained during drying. Application of the active ingredient in liquid form or in a polymeric dilution is the solution of choice for this problem. This may be both done in the first part of the process by soaking a non-woven substrate with the active ingredient which is then laminated between two adhesive layers. These layers subsequently get saturated with active ingredient.

Another possibility is to transfer this technology to a disk-like placing process on the converting line, where printing / soaking with the active solution can be performed just prior to the individualization of the systems. Also, screen printing processes have been tried but to our knowledge these have not yet been used to a significant extent for pharma applications.

Slitting lines

Master rolls which are generated after coating, drying and laminating are slit to narrow rolls which are subsequently transferred to the converting line. A critical, dose-generating role is only included, if products are cut rectangular in the same width. Nearly all transdermal systems are dosed in the subsequent converting step.

Modern Slitting Equipment

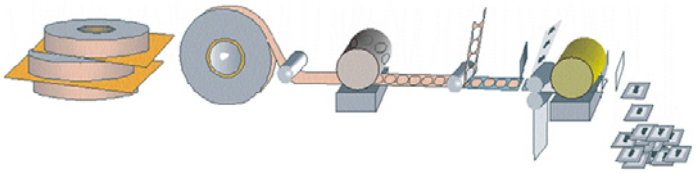


Converting lines

Converting lines may be continuous, rotary-tool based or punching-intermittent in their design. Intermittent designs accept comparatively simple die-cutting tools which provide a well-described, exact pre-defined area and can be easily replaced and changed. As punching occurs in the non-moving phase of the line action, the precision of dosing is very robust and not impaired by machine speed. Rotary processes, however, require precise, product-specific and more expensive tooling which needs a comparatively long time for set-up before production but pays back in higher and reliable speed.

Process validation relies on engineering and machinery-driven IQ/OQ and the product-oriented PQ (process qualification). Challenges of critical parameters in a fully qualified environment in which processing steps are tested under borderline conditions should nowadays be performed under the more flexible conceptual approaches of design-of-experiments (DOE) and adequate reporting. Formal validation batches need to be executed and tested at target conditions and full industrial size.

Rotary Punching and Pouching



Future

For decades it has been expected that iontophoresis, microneedles and sonophoresis will take over and expand the number of molecules suitable for transdermal therapy. This goal looks close now, but will require sophisticated non-standard process technology. As some of these approaches may impair the antibacterial barrier of the skin, sterile or at least low bio-burden technologies will prevail in the future.

Summary

Over forty years of production of modern transdermal systems has led to a quite uniform approach which is shared in practice between a small number of worldwide manufacturers/developers and their Pharma clients. It is advisable for every company with TTS development intentions, to get early access to production knowledge in order to avoid later painful experiences by missing the pharmaceutical targets and specifications.

DRUG DELIVERY LITERATURE

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Provided by Dr. Karsten Cremer

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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.

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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.

MEMBERS OF THE APV DRUG DELIVERY FOCUS GROUP

Karsten Cremer, PhD
Focus Group Leader
Pharma Concepts GmbH, Basel (CH)

Karsten Mäder, PhD
Deputy Focus Group Leader
Martin Luther University, Halle/Saale (D)

Mathew Leigh, PhD
Phares AG, Muttenz (CH)

Johannes Bartholomäus, PhD
Pharmakreativ Consulting, Aachen (D)

Georg Böck, PhD
Boehringer Ingelheim Pharma GmbH & Co. KG
Biberach/Riß (D)

Oskar M. Kalb, PhD
F. Hoffmann-La Roche AG, Basel (CH)

Stefan Bracht, PhD
Bayer Schering Pharma AG, Berlin (D)

Bianca Brögmann, PhD
Evonik Degussa, Darmstadt (D)

Jeffry L. Grunkemeyer, MBA
Patheon International AG, Basel Area (CH)

Michael Horstmann, PhD
tesa SE, Hamburg (D)

Gerben Moolhuizen, MBA
OctoPlus B.V., Leiden (NL)

Thorsten Schmeller, PhD
BASF SE, Limburgerhof (D)

Carsten Timpe, PhD
Novartis Pharma AG, Basel (CH)

Bernd-Ulrich Riebesehl, PhD
Novartis Pharma AG, Basel (CH)

Louise Rosenmayr-Templeton, PhD
Tower Pharma Consulting, Vienna (A)

Jürgen Zirkel, PhD
Lipoid GmbH, Ludwigshafen (D)

Lea Ann Dailey, PhD
Kings College, London (UK)

Achim Göpferich, PhD
University of Regensburg (D)

Contact us!

EDITORIAL GROUP OF THE NEWSLETTER

Editor-in-chief: Dr. Louise Rosenmayr-Templeton, Tower Pharma Consulting, A-Vienna
Compilation and Layout: Christoph Blümer, Catalent Pharma Solutions, D-Schorndorf

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