APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

NEWSLETTER | **ISSUE 01/2005**
INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

READ IN THIS ISSUE:

DRUG DELIVERY EVENTS

Meeting the Needs of Paediatric and Geriatric Patients in Pharmaceutical Development.
Sponsered by the APV Drug Delivery Focus Group.
D-Heidelberg, 29-30 Septermber 2005. *Details...*

1st European Congress on Life Sience Process Technology
D-Nuremberg, 11-13 October 2005. *Details...*

Colloidal Drug Carriers and their Product Applications.
Sponsered by the APV Drug Delivery Focus Group.
D-Berlin, 24-25 November 2005. *Details...*

5th World Meeting on Pharmaceutics and Pharmaceutical Technology
CH-Geneva, 27-30 March 2006. *Details...*

Suggest a meeting to be posted

DRUG DELIVERY PRODUCTS

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Diclac® Schmerzgel (Hexal AG, D-Holzkirchen). Hexal recently received marketing approval in Germany for an OTC, **liposomal formulation** of diclofenac for topical use. A nonsteroidal anti-inflammatory medication (NSAID), diclofenac is used to relieve the pain, tenderness, inflammation (swelling), and stiffness caused by osteoarthritis and rheumatoid arthritis and ankylosing spondylitis.

Suggest a product to be featured

In order to achieve therapeutically effective concentrations of diclofenac in muscles, tendons and joints, the active was encapsulated in liposomes, nanoparticulate vesicles which Hexal claims improve the penetration of the skin. Comprised primarily of phospholipids, a significant component of most cell walls, liposomes are especially well tolerated on the skin and have a low risk of allergic reactions. A further advantage of the liposomal formulation from Hexal is its slow release characteristics, facilitating longer treatment intervals. *Details...*

Triaminic® Thin Strips™ (Novartis Consumer Health, Inc., USA). These **drug-loaded strips** are pocket-size, dissolvable thin films that "melt" on the tongue. Triaminic® Thin Strips™ Cough and Runny Nose contain the antihistamine diphenhydramine for children and are indicated for treating various "cough and cold" symptoms. Triaminic® Thin Strips™ Long Acting Cough contain the cough supressant dextromethorphan.

The dosage form design is rather unusual: thin drug-loaded strips differ from conventional tablets and capsules primarily in that they can be taken without any water. Thus, they present a medicine which is convenient and easy to swallow. The product is targeted at paediatric patients who often have difficulties swallowing traditional solid dosage forms; the formulation design, however, may also be suitable for other groups, such as geriatric patients.

Drug-loaded films or strips based on various biocompatible polymers suitable for oral administration have recently been developed by several drug delivery companies, including LTS Lohmann Therapie-Systeme AG and Lavipharm Corp.

Competing dosage forms which also "melt" in the mouth and can be taken without water include various types of so-called orally disintegrating tablets (e.g. Zomig Rapimelt®, AstraZeneca Inc.) and lyophilised wafers (e.g. Claritin RediTabs®, Schering-Plough HealthCare Products Inc.). *Details...*

DRUG DELIVERY COMPANIES

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Debiopharm SA (CH-Lausanne). Debiopharm is one of four synergistic companies: Debiopharm, Debio Recherche Pharmaceutique (Debio R.P.), Debioclinic and Debioinnovation. Together, these companies carry out integrated drug development.

What is a drug delivery company?
What types of drug delivery companies exist?
Suggest a company to be featured

The Debiopharm Galenic Unit was inaugurated in 2002 in Gland, Switzerland. The Galenic Unit complies with international standards of current Good Laboratory Practices (cGLP) and focuses on feasibility studies, specifically the development of innovative formulations of molecules that Debiopharm has acquired or licensed-in for clinical development. Strengths include solubilization technologies for oral and parenteral administration, and the oral administration of large molecules. The Galenic Unit harnesses innovative technologies such as microemulsions, micelles, liposomes, nanodisperse systems and new polymer-based advanced drug delivery systems, invented in-house, acquired from third parties or developed in collaboration with partners.

Debiopharm: Company Facts

Founded:	1979
Location:	CH-**Lausanne**, Gland, Martigny
Employees:	250
Ownership:	Privately funded
Key technologies:	**DEBIO® PLGA:** Sustained-release PLGA formulation for i.m. and s.c. delivery; drug release through customizable biodegradation rate.
Key technologies in development:	**Debio SPHERE®:** Micro and nanoparticulate technology for oral delivery of macromolecules; blends of biodegradable, polyalctide-co-glycolide (PLGA) and non-biodegradable, positively charged meth-/acrylate copolymers. **DEBIO® PEG**: Polymer bioconjugates of proteins with PEG for i.v. administration. Increased half-life, drug is protected until it reaches the receptors on the surface of target cells.
Product pipeline:	PL-14, Prostate cancer/ Endometriosis, Ph III EPI-hNE4 (DX-890), Cystic fibrosis, Ph II ZT-1, Alzheimer's, Ph II DEBIO-025, AIDS, Ph I
Website:	**www.debio.com**
Contact:	Dr. Evelyne Vuaridel, Debiopharm Galenic Unit Director Tel. +41 (22) 354-8888, Email: evuaridel@debio.com

Debiopharm collaborates closely with Debio R.P., based in Martigny, Switzerland, to develop applications for targeted delivery of controlled-release formulations of medicines. Founded in 1981, Debio R.P. comprises research and development laboratories and an FDA-approved production unit. Debio R.P. has specialized in developing advanced drug delivery systems based on polylactic glycolic acid (PLGA) technology. Microspheres, microcapsules and microgranules are made using coacervation, phase separation, solvent evaporation, spray drying and extrusion. Debio R.P. has also been involved in the development of new biologically active polyethylene glycol derivatives of peptides and proteins.

The first product of Debiopharm is **Decapeptyl ® / Trelstar®**, an analogue of the luteinizing hormone releasing hormone (LHRH or GnRH), in which L-glycine at position 6 has been replaced by D-tryptophan, resulting in a molecule resistant to enzymatic degradation with a higher binding affinity for the GnRH receptors, a prolonged half-life and therefore a greater

potency. Controlled release formulations are available with one and three month release time frames. The product is marketed as Decapepty® by Ipsen and Ferring throughout Europe and is market leader in Southern Europe. In the US and Canada, the product is licensed to Watson Pharmaceuticals (Trelstar®). The other marketed product is **Eloxatin®** (oxaliplatin), a new anticancer chemotherapeutic agent belonging to the platinum complex series. DNA adducts formed by Eloxatin® are bulkier and more hydrophobic than cisplatin adducts. DNA mismatch repair complexes do not recognise DACH-Pt adducts. Eloxatin® was approved in August 2002 by the FDA. The product has been licensed to sanofi-aventis nearly worldwide. The exceptions are Argentina, Uruguay and Paraguay, where it is licensed to Pfizer, in India, where it is licensed to Dr Reddy's Laboratories (Dacotin®), and finally in Japan, where it is licensed to Yakult Honsha.

DRUG DELIVERY COMPANIES

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Phares Drug Delivery AG (CH-Muttenz). Phares, an acronym of **Pha**rmaceutical **Res**earch, was founded in 1985. It is located in the BioValley area near Basle, Switzerland. The company is focused on improving the solubility of poorly water soluble compounds, in order to improve bioavailability.

The 3 main Phares technologies are:
1. SupraVail™ Membrane Lipid Matrix,
2. SupraVail™ Porous Nano Matrix, and
3. SupraVail™ Solid Lipophilic Matrix.

What is a drug delivery company?
Suggest a company to be featured

SupraVail™ Membrane Lipid Matrix makes use of the solubilising effect of monoacyl and diacylphospholipids. The formulation strategy is especially effective with compounds which are lipophilic, because they can interact with the lipophilic domains of the phospholipids. Amphipathic molecules can also be fully solubilised with phospholipids when the charged domains of drug and lipid form stabilising complexes. Finally, SupraVail™ MLM formulations can be manufactured for oral, parenteral and topical routes of administration.

Phares Drug Delivery AG: Company Facts

Founded:	1985
Location:	CH-Muttenz
Employees:	~14
Ownership:	Privately funded
Key technologies:	SupraVail™ - solubilisation technologies for parenteral, topical and oral use
Product pipeline:	Several client products in pre-clinical and clincial testing
Website:	www.phares.biz
Contact:	Jeffry L. Grunkemeyer, Business Development Manager Tel. +41 (61) 317-9049 Email: Jeffry.Grunkemeyer@phares.biz

SupraVail™ Porous Nano Matrix increases the dissolution rate of poorly soluble actives by increasing the specific surface area of the drug. Coated on the surfaces of highly porous particles, the drug also dissolves more quickly because it is often present in an amorphous state. This technology is particularly useful when drug loading is an issue, with loading of up to 50 weight percent. SupraVail™ PNM is suitable for oral and topical applications.

SupraVail™ Solid Lipophilic Matrix is essentially a solid dispersion or coprecipitate technology with a twist: instead of using a typically hydrophilic polymer for the matrix, a hydrophobic / lipophilic polymer is used. Especially useful for compounds with a high tendency to recrystallize, the drug is molecularly dispersed in a matrix with which it can enter into stabilizing hydrophobic-hydrophobic interactions. SupraVail™ SLM is suitable for oral and topical applications.

Phares offers its formulation technology and expertise on a contract / license basis to customers and has recently begun offering a rapid lead selection formulation service.

DRUG DELIVERY PEOPLE

Professor S. S. (Bob) Davis has been working on novel drug delivery systems for almost 30 years and is currently Professor of Pharmaceutical Sciences at the University of Nottingham in the UK. His specific area of expertise includes transmucosal delivery of pharmaceuticals, and oral and parenteral systems for controlled release of pharmaceuticals.

Professor Davis received a Ph.D. in colloid science in 1967 from the University of London and was awarded a one year Fulbright Scholarship to undertake postdoctoral studies at the University of Kansas in the field of solution thermodynamics. He then joined the University of Aston in Birmingham as senior lecturer and head of the Pharmaceutics section; his research there focused on drug delivery systems. After joining the faculty at Nottingham his research broadened to include drug targeting with colloidal carriers, transmucosal delivery, oral and parenteral systems for controlled release and product evaluation through gamma scintigraphy. He has published more than seven hundred papers and is the co-editor of seven books. He is also credited with founding two commercial pharmaceutical organizations, Danbiosyst (UK) Ltd (now part of West Pharmaceutical Services) and Pharmaceutical Profiles Limited.

DRUG DELIVERY TERMINOLOGY

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"Drug Delivery System" (definition provided by Karsten Cremer)

A drug delivery system ("DDS") is a pharmaceutical composition, dosage form, kit, device, or a component thereof which enables the enhanced delivery of an incorporated bioactive compound. *Write a comment on this definition*

Various types of enhancement exist, such as accelerated release, controlled release over time, targeted delivery to specific organs, cells or tissues, utilisation of alternative routes of administration etc.

Example: Implanon® by Organon is an implantable drug delivery system. It delivers the contraceptive, etonogestrel, over a period of 3 years. Release control is achieved by incorporating the active compound in a double-zone matrix of poly(ethylene-co-vinylacetate).

German: "Drug-Delivery-System"
French: *Provide a translation*
Spanish: *Provide a translation*

Suggest a term to be defined
Suggest a definition

"Drug Delivery Company" (definition provided by Karsten Cremer)

A company whose major source of income is derived from selling services, products, or licenses whose value is predominantly based on the application of drug delivery know-how or technologies. *Write a comment on this definition*

The know-how or the drug delivery technologies may be proprietary to the company or not. Product-focused drug delivery companies may market their products themselves (such as Alza Corp.), or they may sell and/or license them to pharmaceutical companies (such as SkyePharma Plc). Service-oriented drug delivery companies sell their R&D services primarily to pharmaceutical or biotech firms (such as OctoPlus Development B.V.).

German: "Drug-Delivery-Firma"; "Drug-Delivery-Unternehmen"
French: *Provide a translation*
Spanish: *Provide a translation*

ABOUT OUR 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. *Read more...*

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LIFE CYCLE MANAGEMENT USING ORALLY DISINTEGRATING DOSAGE FORMS

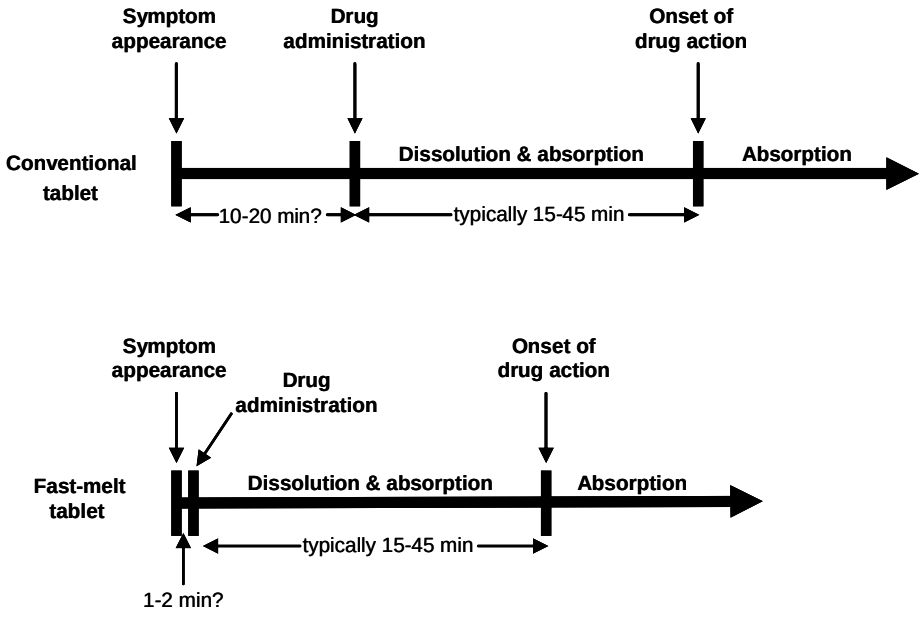
by Karsten Cremer

INTRODUCTION

In recent years, orally disintegrating dosage forms (ODDF) - sometimes referred to as fast-melt tablets - have become increasingly used in the life cycle management of successful product lines in various therapeutic categories. Many patients appreciate the convenience of these formulations which can be taken readily without water whenever symptoms appear. Since they are so easy to swallow, they are particularly attractive for children and elderly people. Pharmaceutical companies, on the other hand, benefit from the product differentiation provided by fast-melting formulations, which are highly valuable in competitive and crowded market segments.

The rationale for line extensions based on fast-melt technologies may differ significantly from product to product. What is perhaps expected or perceived as a major advantage over conventional tablet or capsule formulations is a rapid onset of action. Interestingly, some of the most successful fast-melt formulations in the market are for acute conditions where quick action is most desired, such as Merck's Maxalt-MLT™ and AstraZeneca's Zomig-ZMT™ for migraine headaches, Schering-Plough's Claritin® Reditabs® for allergic reactions, or GlaxoSmith-Kline's antiemetic product, Zofran™ Zydis™. However, fast disintegration of the formulation in the mouth does not automatically lead to a more rapid drug dissolution and absorption. In fact, most fast-melt products, after administration, do not lead to a faster onset of action than the corresponding conventional formulations. Yet, the time from symptom appearance (instead of administration) to drug action may be shorter for fast-melt formulations as, unlike conventional tablets and capsules, they can be taken instantly in almost any situation (see figure 1). Other rationales for fast-melt formulations focus on the ease of swallowing for certain patient groups such as children, elderly people, or psychiatric patients (e.g. Lilly's atypical antipsychotic, Zyprexa® Zydis®), or on improving bioavailability through enhanced buccal absorption (e.g. Abbott's Uprima®).

Figure 1: Time from symptom appearance to onset of drug action for conventional and orally disintegrating formulations



TECHNOLOGIES FOR ORALLY DISINTEGRATING DOSAGE FORMS

Several proprietary and non-proprietary technologies are available for fast-melt formulations, which may be classified in three principal categories: (1) compressed fast-melt tablets, (2) lyophilized forms, and (3) oral films or wafers. While all orally disintegrating dosage forms are solid single units that rapidly disintegrate in the mouth without chewing, they differ substantially in their designs which are used to achieve such disintegration behaviour.

Compressed tablets. Compressed tablets which are designed as fast-melt formulations represent the largest group of technologies offered by the drug delivery industry in this segment. These tablets are typically pressed with lower compression forces than conventional tablets to obtain a higher porosity. Their excipients are optimized for rapid disintegration in minimal volumes of water (saliva) and for maintaining sufficient mechanical strength for packaging and handling by the patients. Most of these tablets disintegrate within about 20 to 30 seconds. Not all of them are mechanically strong enough to be packaged conventionally. They allow the incorporation of relatively high drug loads (doses of up to several hundred milligrams), and taste masking options are offered for several tablet-based fast-melt technologies.

Lyophilized forms. Strictly speaking, lyophilized forms are not tablets, but solid, freeze-dried units having an extremely high porosity which, together with the use of specific excipients, typically leads to a remarkable disintegration time of only about 1 or 2 seconds. On the other hand, lyophilizates are much more friable and moisture-sensitive than most tableted fast-melt formulations; they require special packaging, and will break easily if not handled carefully by patients. Due to their low density, drug doses above approx. 100-200 mg are difficult to accommodate in tablet-size units. The manufacturing process, which is totally different from conventional tabletting, cannot easily be established without significant investments in equipment, so that pharmaceutical companies would typically outsource not only the pharmaceutical development but also the manufacture of the product to specialized drug delivery companies.

Table 1: Important considerations for selecting a fast-melt technology

Category	Desired property	Considerations
Therapeutic effects	Fast onset of action	May not be achievable by fast-melt technologies per se: drug dissolution and absorption tend to be more important than rapid dosage form disintegration
	Buccal/sublingual absorption	May be achievable with any fast-melt dosage form design, but only if drug substance properties are suitable
	Enhanced bioavailability	Ditto
Patient convenience	Fast disintegration	Should be tested with samples representing the envisioned dimensions (depending on drug load!)
	Good mouthfeel	Ditto
	Easy to handle	Certain patient groups may not find it easy to take thin or fragile units from peel packages
	Easy to swallow	Patients having swallowing difficulties may prefer units that are most different from conventional tablets
	Effective taste masking	May require a tablet-based technology if coated drug particles must be incorporated
Life Cycle Management	High degree of product differentiation	Best achieved with designs that are most different from conventional tablets
	Exclusivity / patent protection	Potential exclusivity to be determined for the specific combination of a technology with the drug substance
Costs and risks	Low cost of goods	May require a tablet-based technology
	Standard mfg. equipment	Ditto
	Standard packaging format & materials	Ditto
	Low development costs & risk	Depends on experience and capabilities of technology provider
Other	High drug load	May require a tablet-based technology

Oral films and wafers. These are thin strips of edible, water-soluble polymers which are cut into square, rectangular or disc-shaped units. The strips can be designed to be flexible or rather brittle, opaque or transparent. In their appearance and in patient perception, they differ significantly from conventional dosage forms. They typically disintegrate on the tongue in just a few seconds, which is also a result of their large specific surface area. Among the most important limitations of the dosage form design are the low drug load capacity (doses of more than about 20-30 mg are difficult to incorporate) and the limited taste masking options that are available. Like lyophilizates, oral films are manufactured with highly specialized equipment.

CRITERIA FOR TECHNOLOGY SELECTION

Clearly, none of the presently available dosage form designs meets the requirements of all envisioned fast-melt formulations. A careful analysis of the challenges arising from the combination with a specific drug substance, as well as setting clear priorities within the list of desired product characteristics, is crucial for identifying the best technology match. Some of the considerations which are particularly relevant for fast-melt products are listed in table 1. However, identifying the most suitable technology is only one aspect of successful life cycle management: another one is finding the best partner for providing the technology platform and, most likely, performing a major part of the respective product development program. The experience a drug delivery company has in applying a technology to several different drug candidates, and its capability to run a large-scale development program in accordance with international regulatory standards may significantly contribute to the overall chances for a successful life cycle management project.

CONCLUSION

Orally disintegrating dosage forms represent attractive concepts for the life cycle management of a large number of drug candidates. Several high-profile products have already been successfully developed and introduced to the market. From the various available dosage form designs and technologies, the best match must be identified for every drug candidate separately, taking into account the properties of the drug substance, the desired product characteristics, and the capabilities of the respective technologies and technology providers.

DRUG DELIVERY LITERATURE

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