



# APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER | ISSUE 1/2006

[Focus Group Home](#) | [APV Home](#) | [Disclaimer](#) | [Contact us](#) | [Unsubscribe](#)

## TABLE OF CONTENTS

- ◇ [DRUG DELIVERY EVENTS:](#) Upcoming seminars and conferences
- ◇ [DRUG DELIVERY PRODUCTS:](#) In focus: Macugen<sup>®</sup>, Prialt<sup>®</sup>
- ◇ [DRUG DELIVERY COMPANIES:](#) In focus: LiPlasome Pharma; Novagali Pharma
- ◇ [DRUG DELIVERY TERMINOLOGY:](#) What does "Controlled release" and "Burst release" mean?
- ◇ [DRUG DELIVERY PEOPLE:](#) In focus: Thomas Kissel
- ◇ [FEATURED ARTICLE:](#) Liposomal Parenteral Products - Status anno 2005
- ◇ [DRUG DELIVERY LITERATURE:](#) Recently published reviews in the field of drug delivery
- ◇ [ABOUT OUR FOCUS GROUP:](#) Who are we and what do we do?

## DRUG DELIVERY EVENTS

[BACK TO TABLE OF CONTENTS](#)

### Seminar: Elementary and Applied Pharmacokinetics and Biopharmaceutics

Basle (CH), 14<sup>th</sup>-15<sup>th</sup> March 2006. [Details...](#)

### Seminar: Hard capsules – what are the perspectives of this dosage form?

Freiburg (D), 15<sup>th</sup>-16<sup>th</sup> March 2006. [Details...](#)

### 5th World Meeting on Pharmaceutics and Pharmaceutical Technology

Geneva (CH), 27<sup>th</sup>-30<sup>th</sup> March 2006. [Details...](#)

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

## DRUG DELIVERY PRODUCTS

[BACK TO TABLE OF CONTENTS](#)

**Macugen<sup>®</sup>** (Pfizer). Pfizer received marketing authorization in 2005 for the US in January and for Canada in May for Macugen<sup>®</sup> (pegaptanib sodium injection), for the treatment of neovascular, or "wet," age-related macular degeneration (AMD), a leading cause of blindness.

Pegaptanib, a selective vascular endothelial growth factor (VEGF) antagonist, is a therapeutic aptamer comprised of twenty-eight nucleotides that terminates in a pentylamino linker, to which two 20-kDa monomethoxy polyethylene glycol units are covalently attached via the two amino groups on a lysine residue. The compound was developed by Eyetech Pharmaceuticals, Inc., originally licensed from the University of Colorado in Boulder. Eyetech was acquired by OSI Pharmaceuticals in Nov. 2005. Nektar Therapeutics provides the PEGylation technology for use in Macugen<sup>®</sup>.

The function of the PEGylation in Macugen<sup>®</sup> is not clear from the product literature. In the context of the intraocular route of administration, however, the most likely role of the PEGylation is to improve solubility (and consequently potency) and reduce the elimination rate of pegaptanib from the eye. The product is administered every six weeks by intravitreal injection. In Jan. 2006 OSI announced a licensing deal with PR Pharmaceuticals Inc. to develop a sustained release formulation of Macugen<sup>®</sup>, demonstrating the belief of marketing partners OSI and Pfizer that less frequent intraocular injections would be rewarded by the market. [Details...](#)

**Prialt<sup>®</sup>** (Élan Corporation). In December 2004, Prialt<sup>®</sup> (ziconotide intrathecal infusion) was approved in the US for the management of severe chronic pain in patients for whom intrathecal (IT) therapy is warranted, and approval was granted by the European Commission in February 2005.

Ziconotide is a 25 amino acid, polybasic peptide containing three disulfide bridges with a molecular weight of 2639 Daltons. It is hydrophilic and is freely soluble in water. Prialt<sup>®</sup> is in a class of non-opioid analgesics known as N-type calcium channel blockers. Ziconotide is several orders of magnitude more potent than opiates, and as a non-opioid analgesic it is not subject to the risk of addiction. It is the first new IT analgesic approved in more than two decades.

Interestingly, Ziconotide is approved for use only in the Medtronic SynchroMed<sup>®</sup> EL, SynchroMed<sup>®</sup> II Infusion System and CADD-Micro<sup>®</sup> ambulatory infusion pump, reflecting the importance to the regulatory authorities of having clinically tested both the therapeutic molecule and the drug delivery equipment for the intrathecal route of administration. [Details...](#)

[Suggest a product to be featured!](#)

**LiPlasome Pharma A/S (DK-Lyngby)** was established in 2001 with a mission to develop and commercialize a novel prodrug and drug delivery platform for targeted transport of anticancer drugs.

LiPlasome's drug delivery platform consists of a lipid based drug delivery system (LiPlasomes) for the intravenous transportation of anticancer drugs and prodrugs. The delivery system is formulated with polyethylene glycol (PEG) to prolong the serum half-life of the drugs and prodrugs and avoid the nanocarriers being removed by the reticuloendothelial system.

The key feature of LiPlasome's technology is that it makes use of an endogenous lipid degrading enzyme, secretory phospholipase A2 (PLA2), to achieve specific release of drugs and prodrugs at the tumor target site. PLA2 is present in high concentrations in all human solid tumors investigated to date, such as prostatic, pancreatic, colorectal, gastric, and breast tumors. It belongs to a family of small (14 kDa) interfacially active enzymes that catalyze the hydrolysis of the ester bond in the *sn*-2 position of phospholipids, producing free fatty acids and lysolipids. PLA2 is only weakly active on monomeric lipid substrates but very active on organized lipid substrates such as micelles and liposomes. Furthermore, the enzyme's activity and its mode of action is to a large extent controlled by the physical bio-material properties and in particular the microstructure of the lipid substrate.

LiPlasome aims to make use of these properties of PLA2 to design lipid-based targeted drug delivery systems loaded with cancerchemotherapeutics that are preferentially degraded at the site of the tumor. Its most advanced product is a novel formulation of cisplatin (LiPlaCis) which is in formal tox studies and is planned to enter clinical testing in third/fourth quarter 2006. In addition, LiPlasome aims to use the properties of PLA2 to develop a novel class of lipid based prodrugs which have intrinsic cytotoxic activity upon activation by PLA2 and which can be formulated as prodrug liposomal nanocarriers. In preclinical in vitro studies, LiPlasome showed a pronounced cytotoxic effects on cancer cells secreting phospholipase A2, whereas a negligible effect was observed on normal cells.

#### Factsheet

Founded:	2001
Location:	Denmark – Lyngby (near Copenhagen)
Employees:	7
Ownership:	Privately funded - most recent funding round: March 2005, DKK 45 mio (approx EUR 6.4 mio)
Key Technology	PLA2 activated degradable lipid based nanocarriers; PLA2 is an endogenous lipid degrading enzyme which is expressed specifically in tumours
Pipeline	Conventional chemotherapeutics such as doxorubicin, cisplatin, and methotrexate that are encapsulated and transported to the tumor by the phospholipase A2 degradable liposomes. Status: toxicology testing on-going, clinical trials anticipated in third/fourth quarter 2006  Nanospheres based on proprietary lipid-based systems that have intrinsic anti-tumor activity upon PLA2 activation. Status: in-vitro evaluation.
Website:	<a href="http://www.liplasome.com">www.liplasome.com</a>
Contact:	Dr. Kent Jørgensen, CEO LiPlasome Pharma A/S Technical University of Denmark Building 207 DK-2800 Lyngby Phone (+45) 45252458 Fax. (+45) 45883136 E-mail: <a href="mailto:jorgense@liplasome.com">jorgense@liplasome.com</a>

**Novagali Pharma S.A. (F-Evry)** is a privately-held biopharmaceutical company with a primary focus on ophthalmology and oncology. Novagali's activities are based on its proprietary Novasorb™ and Eyeject™ technologies. Its most advanced products in development are an active ingredient- free formulation as an artificial tear for treatment of dry eye (OTC product), a cyclosporine A formulation for treatment of severe dry eye and an oral paclitaxel formulation for treatment of cancer.

The NOVASORB™ technology is based on formation of cationic (positively charged) emulsions. The positive emulsion droplets can be loaded with active ingredients and are attracted to all biological membranes, including cornea and conjunctiva, that are negatively charged.

Key advantages of the NOVASORB™ cationic emulsions:

- Improved absorption and / or efficacy of drugs
- Improved delivery to all segments of the eye, including the posterior segment (trans-conjunctival-scleral route)
- better wettability properties of the eye surface than eye drops and anionic emulsions, due to a better spreading coefficient on the cornea and conjunctiva.
- protective filmogenic properties; the electrostatic attraction onto the negatively-charged surface of the eye also leads to optimal spreading of the NOVASORB™ cationic emulsion.
- lubrication and protection of the eye surface against mechanical damaging during blinking, ensured by the lipid content of the emulsion

Novagali's nano-emulsion droplets are about 150 nanometers in size and allow the formulation of a wide range of molecules while enhancing their absorption and effectiveness. This technology platform can be applied in many delivery applications, including ocular, oral, injectable and dermatological, and also across a variety of therapeutic areas.

In addition, Novagali is in pre-clinical development with Eyeject™, which consists of specific Novasorb composition designed for eye injections (intravitreal and peri-ocular). Novagali Pharma has demonstrated promising efficacy of intravitreal emulsions in an animal model of posterior uveitis (Experimental Auto-immune Uveitis (EAU)) and is currently working with various compounds to evaluate the safety and length of efficacy of this novel drug delivery system. The main candidates under pre-clinical evaluation are steroids, cyclosporine A and oligonucleotides.

### Factsheet

Founded:	2000
Location:	France – Evry
Employees:	25
Ownership:	Privately funded - most recent funding round: Dec 2004 / Euro 14.2 mio
Key technologies:	Novasorb-tm technology; cationic emulsions technology that improves the delivery of therapeutic levels of drugs to the three segments of the eye: Eye surface, Anterior chamber (trans-corneal route) and Posterior segment (trans-conjunctival-scleral route) The technology can also be used to develop emulsions for injection and oral administration, cream and lotions for dermatology. Eyeject™ ophthalmic emulsions for the intravitreal and peri-ocular administration of <b>lipophilic molecules</b> and negatively charged compounds. The EYEJECT™ technology is under toxicological evaluation
Clinical stage product pipeline:	Cationorm™ (artificial tear): an active-free emulsion for common dry eye. Status: launch expected in 2007. Cyclosporine A eye drop formulation for the treatment of severe dry eye conditions and corticosteroids for the treatment of retinopathies such as macular degeneration. Phase II clinical trials ongoing. A novel formulation of oral delivery of paclitaxel for treatment of cancers. Status: Phase I clinical testing completed
Website:	<a href="http://www.novagali.com">www.novagali.com</a>
Contact:	Dr. Grégory Lambert, VP Research and Development Novagali Pharma S.A. 1, rue Pierre Fontaine Genavenir IV F-91058 Evry, FRANCE Tel: +33 1 69 87 40 20 Fax: +33 1 69 87 40 30 Email: <a href="mailto:contact@novagali.com">contact@novagali.com</a>

**"CONTROLLED RELEASE"** (definition provided by [Karsten Cremer](#))

*The release of an active ingredient from a pharmaceutical composition into a liquid medium in dissolved form according to a predetermined profile. [Write a comment on this definition](#)*

The release kinetics are not defined by the term. For instance, linear (i.e. zero order), first order, and biphasic release kinetics are all examples of controlled release. An antonym is "immediate release", as in "immediate release solid oral dosage forms".

German: ["Kontrollierte Freisetzung"](#)

French: [Provide a translation](#)

Spanish: [Provide a translation](#)

[Suggest a term to be defined](#)

[Suggest a definition](#)

**"BURST RELEASE"** (definition provided by [Karsten Cremer](#))

*A usually undesired initial phase of rapid drug release which does not follow the kinetics of the remaining part of the release profile. [Write a comment on this definition](#)*

The term is most often used for parenteral controlled release products, such as long acting injectable formulations based on polymeric micro particles exhibiting rapid release of a substantial fraction of the dose within the first few hours after administration. If a pronounced phase of rapid drug release occurs at a later stage of drug release, this is usually referred to as "dose dumping".

German: [Provide a translation](#)

French: [Provide a translation](#)

Spanish: [Provide a translation](#)

## DRUG DELIVERY PEOPLE

[BACK TO TABLE OF CONTENTS](#)

**Prof. Dr. Thomas Kissel** studied Pharmacy in Freiburg (Germany) and obtained his professional licence in 1971. He extended his academic training with a study in Chemistry, which he successfully finished in Marburg in 1974 as a diploma chemist. He prolonged his residence in Marburg and obtained a PhD degree in Medical Chemistry in 1976.

He joined the pharmaceutical company Sandoz in Basle (Switzerland) from 1978 until 1991. During this time he had several responsibilities, including the lead of the multidisciplinary drug delivery department.

In 1991, he accepted a position as Full Professor in Marburg. Since this time, he is leading the Institute of Pharmaceutics and Biopharmacy at the Philipps University. His main research areas include biodegradable polymers for the parenteral controlled release, nano-scaled drug delivery systems, peptide drug delivery and polymer-based carriers for DNA delivery. He published around 300 papers in leading international journals. Since 1999 he is director of the "TransMIT center for biopharmaceutical technology".

Prof. Kissel was president of the Controlled Release Society (CRS) in 1998/99. He is the European editor of the Journal of Controlled Release and member of the editorial board of many other journals, including Advanced Drug Delivery Reviews, AAPS Journal, European Journal of Pharmaceutics and Biopharmaceutics, International Journal of Nanomedicine and Journal of Biopharmaceutics and Biotechnology.

In 1998 he received the APV Award together with his former graduate student Dr. Tobias Laich. In 2002 he was honoured with the "Maurice Marie Janot Award" and in the same year with the "CRS Alza Founders Award".



## FEATURED ARTICLE

[BACK TO TABLE OF CONTENTS](#)

### LIPOSOMAL PARENTERAL PRODUCTS - STATUS ANNO 2005

by [PD Dr. P. van Hoogevest](#), [Phares Drug Delivery AG](#), Klünenfeldstrasse 30, CH-4132 Muttenz, Switzerland

#### [INTRODUCTION](#)

Liposomes have been considered for more than 30 years as drug delivery system as part of drug targeting strategies. Active as well as passive targeting strategies, mostly to improve the therapeutic index of drugs for treatment of life threatening diseases were extensively pre-clinically and clinically evaluated. In parallel to this stability issues and large scale production hurdles had to overcome to establish liposomal dosage forms as industrially viable drug delivery systems. During the past five years, gradually a number of liposomal products meeting regulatory and industrial requirements have been introduced on the market. In this paper, the pharmaceutical, technological and clinical properties of these marketed parenteral liposomal drugs are being reviewed.

## MARKETED PARENTERAL LIPOSOMAL PRODUCTS

The following products are to date (2005) on the market in the USA and EU:

1. AmBisome® (Gilead Sciences / Fujisawa Healthcare), Albelcet® (Enzon)  
Membrane intercalated Amphotericin B
2. DaunoXome® (Gilead Sciences)  
Encapsulated Daunorubicin
3. Doxil® (J&J ALZA) and Myocet® (Elan)  
Encapsulated Doxorubicin
4. Visudyne™, Verteporfin for injection; (QLT/Novartis)  
Membrane intercalated Benzoporphyrin
5. Junovan™, for injection; (IDM-Biotech)  
Membrane intercalated Muramyltripeptide-phosphatidylethanolamine

An overview on the formulation characteristics of marketed liposomal dosage forms is given in Table I.

Table I. Characteristics of commercially available liposomal products (2)

Trade name Product/Drug Substance(s) Type of dosage form	Phospholipids and Drug/Lipid ratio	Liposome type Particle size
Albelcet® Amphotericin B Liposomal Suspension	DMPC DMPG 7:3 molar ratio Drug/Lipid 1:1 molar ratio	Probably MLV) <sup>1</sup> , with particle size < 5 µm Opaque in appearance.
AmBisome® Amphotericin B Freeze dried liposomes	213 mg hydrogenated soy phosphatidylcholine 84 mg distearoylphosphatidylglycerol 52 mg Cholesterol 0.64 mg alpha tocopherol Drug/Lipid 1:6 w/w ratio	SUV) <sup>2</sup> , <100 nm
DaunoXome® Daunorubicin citrate Liposomal suspension	Lipid/Drug w/w ratio 18.7:1 Distearoylphosphatidyl- choline and cholesterol (2:1 molar ratio)	SUV, about 45 nm
Doxil® Doxorubicin Liposomes Liposomal suspension Ready-for-use liposomes/ Ammonium gradient	N-(carbonyl-methoxypolyethylene glycol 2000)-1,2- distearoyl-sn-glycero- 3-phosphoethanolamine so- dium salt (MPEG-DSPE), 3.19 mg/mL; fully hydroge- nated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL Drug/Lipid w/w ratio 1:6.	LUV) <sup>3</sup> , 100 nm,
Myocet® Doxorubicin Liposomes Liposomal suspension Three vials; DS vial/liposome/Buffer pH gradient loading	Drug /Lipid 1:4 Egg-PC/cholesterol 1:1 (molar)	OLV) <sup>4</sup> , 180 nm
Visudyne™ Verteporfin® for injection Benzoporphyrin liposomes Freeze dried liposomes	15 mg DS/vial Egg phosphatidyl glycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate and butylated hydroxytoluene, DS/total PL weight ratio of 1 to 7.5 - 15	SUV, Probably smaller than 100 nm
Junovan® Muramyltripeptidephosphati- dyl-ethanolamine (MTP-PE) Freeze dried phospholipids (tert butanol)	DS/Lipid 1:250 w/w POPC/DOPS 7:3 w/w	MLV, 2 -5 µm

)<sup>1</sup> Multilamellar vesicles, )<sup>2</sup> Small unilamellar vesicle, )<sup>3</sup> Large unilamellar vesicle. )<sup>4</sup> Oligolamellar vesicle

Beside these marketed liposomal products, intended for treatment of frequently occurring, diseases, several liposomal drugs have been registered in the US as orphan drugs. Examples are liposomal cyclosporin A, liposomal nystatin, liposomal p-ethoxy growth receptor bound protein-2 antisense product, liposomal prostaglandin E1 injection, Liposomal-cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane-Pt (II) and Liposome encapsulated recombinant interleukin-2 (1).

Table I shows the variety of options to use liposomes technologically and therapeutically. Additionally, the list demonstrates the degree of acceptance of liposomal dosage forms by regulatory authorities, their feasibility for large scale production, and that the products must have sufficient shelf life. More importantly, the liposomal dosage forms should give at least a clinical and /or technical advantage compared to the encapsulated drug resulting in a commercial edge, justifying their acceptance and approval as a product.

## TECHNOLOGICAL ASPECTS

### *Formulation:*

Water soluble, hydrophilic compounds (doxorubicin, daunorubicin) as well as poorly water soluble, lipophilic compounds, (benzoporphyrin) and amphipathic compounds (amphotericin and MTP-PE) can be used in combination with liposomes.

The water soluble compounds are maintained (also in-vivo) in the aqueous interior of the liposomes by a pH gradient (Myocet®), ammonium gradient (Doxil®) or the use of gel state phospholipids in combination with cholesterol (DaunoXome®).

Lipophilic and amphipathic drugs can transfer in vivo from the liposomal membrane to e.g. lipoproteins dependent on their lipid affinity properties. In the liposomal dispersion the drug is associated spontaneously with the liposome because of its affinity for the liposomal membrane.

The phospholipids used are mainly synthetic phospholipids. Egg-PC and hydrogenated Soy PC are also used. Natural Soy PC can also be considered as it is employed at high levels as an emulsifier in emulsions for parenteral nutrition and in parenteral mixed-micellar formulations.

The drug load in most formulation is such that at therapeutic doses of the used drug the equal or about twenty fold the amount of drug is co-administered as phospholipids. In case of the MTP-PE liposomes, the 250 fold excess of phospholipid to drug is used to maintain the MTP-PE with the liposomal structure after iv administration (MTP-PE without phospholipids is more toxic) and to administer a high number of liposomes able to reach a high number of macrophages.

The liposomal products are either ready for use aqueous liposomal dispersions or freeze dried liposomes. This illustrates that, when the chemical stability of the drug substance it allows, liposomal dosage forms have sufficient chemical and physical stability and shelf life for commercial use.

The particle sizes, lamellarity and morphology of the used liposomes show that any liposome type (SUV, LUV, OLV and MLV) is suitable for commercial development.

### *Manufacturing:*

Exact details of the manufacturing of commercial liposomal products are of course not published. However, based on available literature on large scale manufacturing methods of liposomes and characteristics of the liposomes the following can be assumed.

Use of water soluble drugs (doxorubicin and daunorubicin) in combination with small liposomes typically requires high shear homogenisation and or extrusion of the phospholipid dispersion. The encapsulation of the water soluble drugs is driven by a pH shift (Myocet®) or ammonium gradient (Doxil®). This is achieved in the case of Myocet® by means of a multistep in-situ constitution procedure, whereas the Doxil® liposomes are loaded with doxorubicin on a large scale. In the case of DaunoXome®, the non-encapsulated drug must have been removed on large scale by e.g. dialysis. To guarantee the sterility of aqueous liposomal suspensions, the manufacturing should be done under aseptic conditions and final aseptic filtration should be performed.

Incorporation of lipophilic/amphipathic drugs (amphotericin, benzoporphyrin, MTP-PE) in the liposomal bilayer has likely been done by co-dissolving the components in a solvent followed by a drying step to remove the solvent. The resulting drug-lipid complex is hydrated and subjected to homogenisation steps. When this step is mild, MLV will result, when this step is done under high pressure then small liposomes will result. In case the liposomes are unstable (note: limiting will be the drug not the phospholipids !!) the drug loaded liposomes are freeze dried.

The liposomal dosage form for MTP-PE is prepared by dissolving the formulation components in tert-butanol followed by sterile filtration and removal of the tert-butanol by lyophilisation. Shortly before use, the multilamellar liposomes are in-situ prepared by adding an aqueous medium to the lyophilisate and shaking by hand (3).

## CLINICAL ASPECTS

In general, liposomal drugs are intravenously administered by slow infusion at relatively low phospholipid concentrations. In order to eliminate a residual embolism risk, it is recommended to infuse such parenteral dispersions through a safety filter with an average pore size diameter of 3 -5 µm.

Albelcet® undergoes rapid reticuloendothelial (Mononuclear Phagocytotic System) uptake from the circulation and achieves significantly higher tissue concentrations in the liver, spleen and lung compared to comparably dosed conventional amphotericin B (4). Albelcet® is less nephrotoxic than conventional AmB (mixed micelle) and can be given safely to patients with pre-existing renal impairment. The most commonly reported adverse effects are transient infusion-related events, including chills, fever, nausea and vomiting. Comparative studies suggest that Albelcet® is a cost-effective treatment option compared with conventional AmB or other lipid-based formulations of amphotericin B (5,6).

AmBisome®, has an opposite action mechanism. It has a long circulating half-life of 5-24 h in animals, and in animal models appears to localize at sites of infection in the brain (cryptococcosis, aspergillosis, coccidioidomycosis), lungs (blastomycosis, paracoccidioidomycosis, aspergillosis) and kidneys candidosis), delivering amphotericin B that remains bioavailable in tissues for several weeks following treatment (7).

Doxil® liposomes with doxorubicin are THE classical example of a major step towards active drug targeting. Due to the presence of PEG-ylated phospholipid in the membrane, the liposomes are only very slowly taken up by macrophages and are able to circulate in the vascular compartment (MRT of 4 days) till they reach a site of increased vascular permeability (compromised and chaotic vasculature) caused by a tumor. The liposomes and their cargo, doxorubicin, extravasate and release gradually the doxorubicin at the desired site of action. Single dose limiting toxicity of Doxil® is mucositis/stomatitis, whereas multiple dose limiting toxicity is palmar-plantar erythrodysesthesia (hand-foot syndrome).

The Myocet® liposomes with doxorubicin targets encapsulated drug rapidly to MPS. As a result peak plasma levels are avoided. It is assumed that a "MPS Depot" is created from which drug re-enters blood stream to mimic a slow infusion. Plasma and tissue AUC are comparable to the same dose of doxorubicin HCl aqueous solution. Dose limiting toxicity of single and multiple doses is myelosuppression, most notably neutropenia (8).

The Daunorubicin citrate liposome (DaunoXome®) contains daunorubicin encapsulated in small liposomes having a lipid composition, which is quite stable in the blood circulation. DaunoXome® is indicated as a first line cytotoxic therapy for advanced HIV-associated Kaposi's sarcoma. The liposomes have a circulation time between these of Moycet® and Doxil® (9). In comparison with free daunorubicin, DaunoXome® shows a low volume of distribution, a lower clearance and a lower interindividual variability in these parameters (10). The observed dose-limiting toxicities of therapeutic doses of DaunoXome®, myelosuppression (especially granulocytopenia), fatigue, and nausea and vomiting ([www.fda.gov](http://www.fda.gov))

In general, one of the key toxicity issues linked to the use of free doxorubicin and daunorubicin is that of both an acute and a chronic form of cardiomyopathy. This is circumvented by the use of the liposomal formulations (11).

In the case of benzoporphyrin liposomes (Verteporfin® for injection) the liposomes act as solubiliser for the highly lipophilic benzoporphyrin. The lipophilic benzoporphyrin is able to transfer from the liposomal membrane to other lipidic domains in the blood circulation (12,13). In turn, the lipoproteins loaded with the drug, transport the drug substance to the sites of macular degeneration inflammation, which have an increased expression of lipoprotein receptors.

Junovan™ (Mepact™) (MTP-PE liposomes), activates macrophages in vivo in order to increase their capacity to destroy cancer cells (particularly metastases). Due to their large size and negatively charge the liposomes are rapidly taken up by their target cells, the macrophages. In addition, the liposomal MTP-PE has a much better therapeutic index than the free MTP-PE which forms micelles (14). Mepact™ has received orphan drug status for treatment of osteosarcoma (the most common type of bone cancer, which primarily affects adolescents) and Ewings Sarcoma in the United States, and in Europe. A Phase III clinical trial has been completed which included close to 800 patients over a six-year period.

## CONCLUSIONS

Liposomal dosage forms are clearly nowadays the golden standard for active and passive drug targeting of both water soluble and water insoluble drugs to increase the therapeutic index of these drugs. Also, they will play increasingly a role as solubilising dosage forms for water insoluble drugs. They have passed the hurdles of regulatory approval and technical, toxicological and clinical validation and should therefore be considered by industry as the first choice in case the therapeutic index of a drug needs to be improved.

However, since the preparation and characterization of liposomal dosage forms is quite challenging, the use of such dosage form in pre clinical industrial research in combination with NCE's is quite limited. Therefore, the potential of such combinations are not adequately explored at an early research stage. In order to fill this gap, in a next contribution to the APV newsletter, several methods to prepare liposomes conveniently for pre clinical research are presented. Additionally, in case of water insoluble drugs, these methods allow also oral administration of such drugs to maximize oral bioavailability.

## REFERENCES

1. [www.fda.gov/orphan/designat/list.htm](http://www.fda.gov/orphan/designat/list.htm)
2. [www.fda.gov](http://www.fda.gov)
3. Van Hoogevest, P. and Fankhauser, P. An industrial liposomal dosage form for muramyl-tripeptide-phosphatidyl ethanolamine (MTP-PE). In: "Liposomes in the Therapy of Infectious Diseases and Cancer", (Eds. Fidler, I.J. and Lopez-Berestein, G.), Alan R. Liss Inc., New York, 1989, 453.
4. Linden, P.K., Expert Opin Pharmacother. Amphotericin B lipid complex for the treatment of invasive fungal infections. 2003, 4(11), 2099-110.
5. Martino, R., Efficacy, safety and cost-effectiveness of Amphotericin B Lipid Complex (ABLC): a review of the literature. AmBisome® has the same clinical profile as Albelcet® but the treatment costs are on debate. Curr Med Res Opin 2004, 20(4), 485-504.
6. Veerareddy, P.R., Vobalaboina V., Lipid-based formulations of amphotericin B. Drugs Today (Barc). 2004, 40(2), 33-45.
7. Adler-Moore, J., Proffitt, R.T., AmBisome: liposomal formulation, structure, mechanism of action and pre-clinical experience. J Antimicrob Chemother. 2002, 49 Suppl 1, 21-30.
8. [www.fda.gov/ohrms/dockets/ac/01/slides/3763s2\\_08\\_martin/index.htm](http://www.fda.gov/ohrms/dockets/ac/01/slides/3763s2_08_martin/index.htm)
9. Allen, T.M., Martin F.J., Advantages of liposomal delivery systems for anthracyclines. Semin Oncol. 2004, 31(6 Suppl 13), 5-15.
10. Hempel, G., Reinhardt, D., Creutzig, U., Boos, J., Population pharmacokinetics of liposomal daunorubicin in children. Br J Clin Pharmacol. 2003, 56(4), 370-7.
11. Waterhouse D.N., Tardi P.G., Mayer L.D., Bally M.B. A comparison of liposomal formulations of doxorubicin with drug administered in free form: changing toxicity profiles, Drug Saf. 2001, 24(12), 903-20.
12. Chowdhary, R.K., Shariff, I., Dolphin, D., Drug release characteristics of lipid based benzoporphyrin derivative. J. Pharm. Pharmaceut. Sci. 2003, 6, 13-19.
13. Fahr, A., Van Hoogevest, P., May, S., Bergstrand, N., Leigh, M.L.S., Transfer of lipophilic drugs between liposomal membranes and biological interfaces: Consequences for drug delivery Eur J. Pharm Sci 2005, in press
14. Schumann, G., Van Hoogevest, P., Fankhauser, P., Probst, A., Peil, A., Court, M., Schaffner, J.C., Fischer, M., Skripsky, T. and Graepel, P., Comparison of free and liposomal MTP-PE: Pharmacological and toxicological aspects. In: "Liposomes in the Therapy of Infectious Diseases and Cancer", (Eds. Fidler, I.J. and Lopez-Berestein, G.), Alan R. Liss Inc., New York, 1989, 191.

## DRUG DELIVERY LITERATURE

[BACK TO TABLE OF CONTENTS](#)

### RECENTLY PUBLISHED LITERATURE REVIEWS IN THE FIELD OF DRUG DELIVERY:

#### **Local inner-ear drug delivery and pharmacokinetics.**

Salt AN, Plontke SK. Drug Discov Today. 2005 Oct 1;10(19):1299-306.

#### **Gastrointestinal stromal tumors and the evolution of targeted therapy.**

Sanborn RE, Blanke CD. Clin Adv Hematol Oncol. 2005 Aug;3(8):647-57.

#### **New targeted approaches in chronic myeloid leukemia.**

Cortes J, Kantarjian H. J Clin Oncol. 2005 Sep 10;23(26):6316-24.

#### **Cell delivery system: a novel strategy to improve the efficacy of cancer immunotherapy by manipulation of immune cell trafficking and biodistribution.**

Okada N. Biol Pharm Bull. 2005 Sep;28(9):1543-50.

#### **The role of blood-brain barrier permeability in brain tumor imaging and therapeutics.**

Provenzale JM, Mukundan S, Dewhirst M. AJR Am J Roentgenol. 2005 Sep;185(3):763-7.

#### **Transfer of lipophilic drugs between liposomal membranes and biological interfaces: consequences for drug delivery.**

Fahr A, van Hoogevest P, May S, Bergstrand N, S Leigh ML. Eur J Pharm Sci. 2005 Nov;26(3-4):251-65.

#### **Drug eluting stents in interventional cardiology -- current evidence and emerging uses.**

Swanson N, Gershlick AH. Curr Drug Targets Cardiovasc Haematol Disord. 2005 Aug;5(4):313-21.

#### **Lipid carrier systems for targeted drug and gene delivery.**

Hashida M, Kawakami S, Yamashita F. Chem Pharm Bull (Tokyo). 2005 Aug;53(8):871-80.

#### **Local antibiotic delivery systems: where are we and where are we going?**

Hanssen AD, Osmon DR, Patel R. Clin Orthop Relat Res. 2005 Aug;(437):111-4.

#### **Novel advances in drug delivery to brain cancer.**

Lesniak MS. Technol Cancer Res Treat. 2005 Aug;4(4):417-28.

#### **Nanotechnology-based drug delivery for cancer.**

Jain KK. Technol Cancer Res Treat. 2005 Aug;4(4):407-16.

#### **Targeted drug delivery in cancer therapy.**

Vasir JK, Labhasetwar V. Technol Cancer Res Treat. 2005 Aug;4(4):363-74.

**The virosome concept for influenza vaccines.**

Huckriede A, Bungener L, Stegmann T, Daemen T, Medema J, Palache AM, Wilschut J. *Vaccine*. 2005 Jul 8;23 Suppl 1:S26-38.

**Therapeutic potential of nanoparticulate systems for macrophage targeting.**

Chellat F, Merhi Y, Moreau A, Yahia L. *Biomaterials*. 2005 Dec;26(35):7260-75.

**'Smart' delivery systems for biomolecular therapeutics.**

Stayton PS, El-Sayed ME, Murthy N, Bulmus V, Lackey C, Cheung C, Hoffman AS. *Orthod Craniofac Res*. 2005 Aug;8(3):219-25.

**Recent advances in small molecule drug delivery.**

Kidane A, Bhatt PP. *Curr Opin Chem Biol*. 2005 Aug;9(4):347-51.

**Cell-penetrating peptides: tools for intracellular delivery of therapeutics.**

Deshayes S, Morris MC, Divita G, Heitz F. *Cell Mol Life Sci*. 2005 Aug;62(16):1839-49.

**A novel foam vehicle for delivery of topical corticosteroids.**

Huang X, Tanojo H, Lenn J, Deng CH, Krochmal L. *J Am Acad Dermatol*. 2005 Jul;53(1 Suppl 1):S26-38.

**Nanovector therapeutics.**

Ferrari M. *Curr Opin Chem Biol*. 2005 Aug;9(4):343-6.

**Pharmacological approach to evaluate aerosol pulmonary deposition.**

Girodet PO, Molimard M. *J Aerosol Med*. 2005 Summer;18(2):183-92.

**Targeted therapy for colorectal cancer: mapping the way.**

Mocellin S, Lise M, Nitti D. *Trends Mol Med*. 2005 Jul;11(7):327-35.

**Strategies for cytosolic delivery of liposomal macromolecules.**

Fretz MM, Mastrobattista E, Koning GA, Jiskoot W, Storm G. *Int J Pharm*. 2005 Jul 25;298(2):305-9.

**Roles of the conjunctiva in ocular drug delivery: a review of conjunctival transport mechanisms and their regulation.**

Hosoya K, Lee VH, Kim KJ. *Eur J Pharm Biopharm*. 2005 Jul;60(2):227-40.

**Human respiratory epithelial cell culture for drug delivery applications.**

Forbes B, Ehrhardt C. *Eur J Pharm Biopharm*. 2005 Jul;60(2):193-205. Epub 2005 Apr 21.

**Transdermal iontophoresis: combination strategies to improve transdermal iontophoretic drug delivery.**

Wang Y, Thakur R, Fan Q, Michniak B. *Eur J Pharm Biopharm*. 2005 Jul;60(2):179-91.

**Malaria parasite transporters as a drug-delivery strategy.**

Biagini GA, Ward SA, Bray PG. *Trends Parasitol*. 2005 Jul;21(7):299-301.

**Delivery aspects of small peptides and substrates for peptide transporters.**

Steffansen B, Nielsen CU, Frokjaer S. *Eur J Pharm Biopharm*. 2005 Jul;60(2):241-5.

**Colloidal carriers and blood-brain barrier (BBB) translocation: a way to deliver drugs to the brain?**

Garcia-Garcia E, Andrieux K, Gil S, Couvreur P. *Int J Pharm*. 2005 Jul 25;298(2):274-92.

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 pharmaceuticals. [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...](#)

**MEMBERS OF THE APV DRUG DELIVERY FOCUS GROUP**

**Karsten Cremer, PhD (Group Leader)**  
 Founder and Principal  
 Pharma Concepts GmbH  
 Basel, Switzerland

**Rainer Alex, PhD**  
 Global Coordinator  
 Pharmaceutical and Analytical R&D  
 Hoffmann-LaRoche AG  
 Basel, Switzerland

**Johannes Bartholomäus, PhD**  
 Head of Pharmaceutical Development  
 Grünenthal GmbH  
 Aachen, Germany

**Stefan Bracht, PhD**  
 Head of Early Development and Drug Delivery Systems  
 Pharmaceutical Development  
 Schering AG  
 Berlin, Germany

**Helmut Fricke, PhD**  
 Consultant  
 Hamburg, Germany

**Gerben Moolhuizen, MBA**  
 Business Development Manager  
 OctoPlus B.V.  
 Leiden, Netherlands

**Jeffry L. Grunkemeyer, MBA**  
 Business Development Manager  
 Phares Drug Delivery AG  
 MuttENZ, Switzerland

**Karsten Mäder, PhD**  
 Professor of Pharmaceutics  
 Martin-Luther-University  
 Halle, Germany

**Jörg Ogorka, PhD**  
 Head of Life Cycle Management  
 Novartis Pharma AG  
 Basel, Switzerland

**Gerhard Renner, PhD**  
 Business Director Technology  
 Degussa Pharma Polymers  
 Darmstadt, Germany

[Contact us!](#)

**Disclaimer:**

This newsletter is provided "as is" and without warranty, express or implied. All warranties with regard to the accuracy, reliability, timeliness, usefulness or completeness of the information contained in the news-letter are expressly disclaimed. All implied warranties of merchantability and fitness for a particular use are hereby excluded. None of the information provided in the newsletter constitutes, directly or indirectly, the practice of medicine, the dispensing of medical services, the recommendation to buy or use a product. External links are provided in the newsletter solely as a convenience and not as an endorsement of the content on such third-party websites. The APV Drug Delivery Focus Group is not responsible for the content of linked third-party sites and does not make any representations, warranties or covenants regarding the content or accuracy of materials on such third-party websites. If you decide to access linked third-party websites, you do so at your own risk.