



APV Focus Group Drug Delivery

Combining Science & Technology to Create Advanced Drug Delivery Systems

INTERNATIONAL ASSOCIATION FOR PHARMACEUTICAL TECHNOLOGY

NEWSLETTER | ISSUE 2/2007

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DRUG DELIVERY EVENTS

Provided by Christoph Blümer

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Pharmaceutical Technology Annual Conference 2007

Philadelphia, PA (USA), July 24th to 26th 2007

[Details](#)

16th International Symposium on Microencapsulation

Lexington, Kentucky (USA), September 9th to 12th 2007

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The 14th Intermediate Workshop on Pharmacokinetic/Pharmacodynamic Data Analysis: A Hands-on Course Using WinNonlin

Cologne, Germany, September 16th to 20th 2007

[Details](#)

APV Course: Innovative Drug Delivery Technologies for the Enhancement of Bioavailability

Hirschberg/Heidelberg (D), September 27th to 28th 2007

[Details](#)

APV Course: Novel Excipients or Novel Use of known excipients from technical Feasibility to Registration

Berlin (D), December 11th to 12th 2007

[Details](#)

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

DRUG DELIVERY PRODUCTS

Provided by Dr. Louise Rosenmayr-Templeton

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Supprelin™-LA (Indevus Pharmaceuticals): In May 2007 the FDA approved Supprelin™-LA, a subcutaneous implant containing 50 mg of the gonadotrophin releasing hormone analogue, histrelin acetate, for the treatment of central precocious puberty (CPP). Children with CPP experience early onset of secondary sexual characteristics and show advanced bone maturation that can result in them not attaining their potential adult height. Supprelin™-LA is currently the only approved product that in one administration affords year long treatment for this condition which annually affects 1 to 2 children per 10,000 in the US. The US CPP market is estimated to be worth approximately \$80 million, and is currently dominated by TAP's Leupron™ Depot PED which is administered every four weeks.

The implant exploits the company's Hydron™ technology, and is designed to release the drug at an approximate rate of 65 mcg/day over a 12 month period. Indevus acquired the Hydron™ technology when they bought Valera Pharmaceuticals in April 2007. The implant consists of a drug core contained within a 3.5 cm by 3 mm cylindrical hydrogel reservoir, produced when proprietary blends of non-biodegradable polymers are spin cast. Drug release is via pores in the hydrogel wall and therefore is dependent on drug solubility, polymer blend composition and implant wall attributes.

The hydrogel reservoir is composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16 and Triton X-100. The drug core also contains stearic acid. The hydrated implant is stored in 1.8% NaCl solution so that it is primed for drug release upon insertion. It is inserted and removed surgically under local anesthetic.

More information at <http://www.indevus.com>

Tovalt™ ODT 5 mg and 10 mg tablets (Biovail Corporation): Tovalt™ ODT 5mg and 10 mg tablets obtained FDA approval in April 2007. These tablets contain the short-acting sedative/hypnotic, Zolpidem tartrate, in a proprietary rapidly disintegrating formulation. This drug, which is licensed for the treatment of short-term insomnia, came off patent in Oct 2006. The drug generated US sales of \$2 billion in 2005 for its originator, Sanofi-Aventis, and was originally developed as a standard release tablet (Ambien™/Stilnoct™).

Biovail is not the only manufacturer interested in tapping into the Zolpidem market. Over 10 manufacturers received ANDA approvals for Zolpidem in April and a generic version is already on sale in Europe. In addition, Sanofi-Aventis brought out a sustained release version of its product in 2005. Biovail hope that their novel formulation will give them a competitive edge over straight generic versions of Ambien™, by meeting the needs of the reported 40 % of adults who have problems swallowing.

The tablets contain Zolpidem tartrate encapsulated in microparticles produced using Biovail's CEFORM™ (Centrifugally Extruded and Formed Microspheres) technology which produces uniform spheres in the 50-600 micron size range. Since Zolpidem has poor aqueous solubility, the excipient, Stearoyl Macrogolglycerides, is included to improve drug dissolution. The particles are then coated to provide taste-masking before being incorporated into a Flashdose™ tablet formulation containing crospovidone as a disintegrant. This directly compressible formulation allows disintegration in the mouth within seconds with or without water.

More information at <http://www.biovail.com>

DRUG DELIVERY COMPANIES (I)

Provided by Gerben Moolhuizen

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Camurus AB (SE-Lund)

Fact sheet

Founded:	1991
Location:	Lund, Sweden
Employees:	25
Ownership:	Privately funded
Key technologies:	Camurus has two lipid-based technologies, based on the use of phospholipid, glycerolipids, and optionally cosolvents:

FluidCrystal®: non-aqueous, low-viscous, injectable liquid, forming a liquid crystalline (LC) depot in sc/im and other tissues and on topical and mucosal surfaces, from which the drug is slowly released. The low viscosity of the injectable formulations permits the use of very thin needles (25 gauge is standard) and the high solubilizing capacity with drug payloads of up to 30% allows smaller injection volumes. The initial burst is minimal thanks to rapid structure formation. The biocompatible lipid matrix is safely degraded during drug release. Furthermore, the system has been shown to give stable plasma levels of peptides.

FluidCrystal® nanoparticles (NP): liquid crystalline nanoparticles, comprising cubic, hexagonal or sponge inner phases, for oral, topical or iv delivery. The mean particle size can be controlled between 50-500 nm and drug payloads up to 40% (by excipient weight) have been established for small molecule drugs. The size and surface coating of FluidCrystal® NP facilitate control of intravenous circulation times. By use of specific coatings recognition by the immune system can be regulated and the macrophageal uptake minimized. This enables enhanced circulation and the potential to improve the targeting of disease-specific areas of the body.

Product pipeline:	License agreements or collaborations are ongoing with over ten European, Japanese and US companies, several projects have reached clinical phase, and two products have reached the market after being developed by Camurus (Elyzol by Colgate-Palmolive, and Salinum by Sinclair Pharm.) Camurus has also an in-house product development pipeline, with three products under clinical evaluation;
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CAM2028 is a mucoadhesive, extended-release formulation of benzydamine, a local anaesthetic with anti-inflammatory and antibacterial properties, designed for the treatment of oral mucositis in cancer patients. CAM2028 aims to provide an extended analgesic effect as well as protection for damaged mucosal surfaces. The product is based on the proprietary FluidCrystal® drug delivery system and is administered as a lipid-based solution that spreads across damaged mucosal surfaces. Directly after administration, CAM2028 forms a mucoprotective and drug encapsulating liquid crystal gel, providing extended release of benzydamine.

Camurus AB has recently received approval to begin a Phase II proof-of-concept clinical trial of CAM2028 for the treatment of pain in oral mucositis.

CAM2029 is a long-acting injectable depot of octreotide acetate. Octreotide is a synthetic analogue of somatostatin, a naturally occurring hormone peptide that signals to the pituitary to reduce growth hormone production. In clinical practice the compound is used to treat acromegaly and the carcinoid syndrome by controlling hormonal hypersecretion.

Camurus recently announced results of a Phase I trials of CAM2029. The clinical study, which has enrolled 32 healthy volunteers, has been designed for assessment of tolerability, pharmacokinetics, and pharmacodynamics. This is a double-blind, randomised, placebo-controlled, single dose study of three different dose volumes of octreotide, given by subcutaneous injection, and one dose volume by intramuscular injection.

CAM2032 is a new depot formulation of the market leading LHRH agonist leuprolide (leuprorelin acetate) combined with Camurus' delivery system FluidCrystal®. Camurus has recently received approval to initiate a Phase I/II clinical trial of CAM2032 for prostate cancer. The clinical trial is a single-dose, dose-escalating, open-label, multi-centre, cohort trial performed to determine the leuprolide drug serum profile and the serum testosterone suppressing effects after a single subcutaneous administration of three different doses of CAM2032. 24 male patients with advanced/metastatic prostate cancer will complete the trial. Assessment of safety of the investigational product CAM2032 is a further key objective of this clinical trial.

Website: <http://www.camurus.se>

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DRUG DELIVERY COMPANIES (II)

Provided by Jeffrey L. Grunkemeyer

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pSivida Limited (Perth, Australia; Malvern, UK; and Watertown, MA, USA) describes itself as "a global bio-nanotech company committed to the development of drug delivery products in the healthcare sector, initially in ophthalmology and oncology."

The first two approved products of pSivida – Vitrasert® and Retisert® – are sustained release back of the eye treatments for chronic eye disease. The products are intravitreal drug implants designed to deliver sustained levels of drug directly to the back of the eye for a period of up to 30 months. Both products are marketed and sold by the global ophthalmology company, Bausch & Lomb.

pSivida's strategic focus is in the rapidly growing market for new drug delivery formulations. Improvements in drug delivery should improve patient safety and drug bioavailability. Additionally, the use of drug delivery systems is of strategic value to global pharmaceutical companies, who want to enable the delivery of new drugs while also extending the commercial life of their current drugs.

Fact sheet

Founded:	2000
Locations:	Perth, Australia; Malvern, UK; and Watertown, MA, USA
Employees:	55
Ownership:	Publicly listed on ASX:PSD, DAX:PSI and NASDAQ:PSDV
Key technologies:	Durasert™ Technology: drug-containing core and one or more polymer layers, membranes or coatings, that deliver drugs locally or systemically at a controlled rate for a predetermined period of time ranging from days to years. BioSilicon™ Technology: BioSilicon on or in the body. pSivida holds granted patents in various healthcare applications, including our core focus of specialized drug delivery, targeted internal cancer therapy, diagnostics and the use of silicon in pharmaceuticals and food. The lead oncology product, BrachySil is protected by this series of patents and patent applications. CODRUG™ Technology: the use and delivery of codrugs for various pharmaceutical- and healthcare-related applications. Other Technology: various other technologies, including treatment of otic disorders and methods for controlling elevated intraocular pressure.

Product pipeline: **Medidur™** is an injectable non-erodible intravitreal device for the treatment of Diabetic Macular Edema (DME), a leading cause of vision loss for people under the age of 65. The implant releases a constant amount of fluocinolone acetonide to the back of the eye and is designed to have a duration of between 18 to 36 months. The product is being co-developed and will be marketed together with Alimera Sciences.

The Medidur insert is only 3mm in length and 0.37mm in diameter and is delivered via a 25 gauge injector system during an in-office procedure. At either 0.2 or 0.5 micrograms of drug delivered to the retina per day, Medidur will be releasing the smallest amount of drug currently available for treating DME. The product is currently in Phase III clinical trials. Medidur has been granted fast track by the FDA, and European registration filing is expected in the first half of 2009. It was announced in April 2007 that pSivida had licensed Medidur to Pfizer for all ophthalmic applications.

BioSilicon™ drug delivery technology in the next generation of drug delivery treatments to the back of the eye.

BrachySil™ for brachytherapy treatment for operable and inoperable tumours. 32-P isotope has a short active range resulting in less damage to healthy tissue, and the 32-p device is immobilized in the tumor, significantly reducing risk of leakage or systemic side effects. BrachySil is delivered under local anaesthetic via fine gauge needle, and patients can be discharged the next day. 32-P half-life of 14 days allows more convenient distribution to hospitals and application in the patient.

Clinical evaluation of BrachySil in man has shown evidence of safety and tumour regression. Phase IIa clinical trials for BrachySil as a potential new brachytherapy treatment for inoperable liver cancer have demonstrated safety and good tolerability. Furthermore, significant tumour regression was achieved with a maximum regression of 100 percent in some smaller tumours treated as determined by CT scanning.

Website: <http://www.psivida.com>

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DRUG DELIVERY TERMINOLOGY

Provided by Dr. Karsten Cremer

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Liposome

A microvesicle composed of one or more bilayers of lipidic amphipathic molecules typically enclosing an equal number of aqueous compartments. [Write a comment](#)

Liposomes form spontaneously when amphipathic lipids capable of bilayer formation, such as phosphatidylcholines, are dispersed in water. To generate liposomes with a defined size distribution and morphology, various methods can be used, e.g. ultrasonication, high pressure homogenisation and extrusion through filter membranes. Examples of subtypes of liposomes differentiated by their size and lamellarity are small unilamellar vesicles (SUV, approx. 60 to 150 nm), large unilamellar vesicles (LUV, approx. 150 to 10,000 nm) and multilamellar vesicles (MLV, approx. 100 to 10,000 nm). Liposomes may encapsulate hydrophilic and lipophilic compounds.

German: [Liposom](#)
French: [Liposome](#)
Spanish: [Provide a translation](#)

[Suggest a term to be defined](#)
[Suggest a definition](#)

Micelle

A colloidal aggregate of surface-active molecules dispersed in a liquid phase. [Write a comment](#)

Micelles are often spherical, but may also be cylindrical or ellipsoid in shape. They form spontaneously when surfactants are dispersed in a liquid above their critical micelle concentration (CMC). The stability of micelles is typically much lower than that of liposomes: when the continuous liquid phase is diluted below the CMC, micelles tend to dissociate. Special subtypes of micelles are mixed micelles (comprising a surfactant and a co-surfactant) and inverse micelles (with a core formed by the hydrophilic groups of the surfactant molecules, whereas the hydrophobic groups form the "shell"). In pharmaceuticals, micelles are most often used for the solubilisation of poorly soluble compounds.

German: [Mizelle](#)
French: [Micelle](#)
Spanish: [Provide a translation](#)

Robert S. Langer is one of 13 Institute Professors (the highest honor awarded to a faculty member) at the Massachusetts Institute of Technology (MIT).

Over 900 articles and nearly 550 issued or pending patents worldwide (one of which was cited as the outstanding patent in Massachusetts in 1988 and one of 20 outstanding patents in the United States) mark his successful career in science. His patents have been licensed or sublicensed to over 180 pharmaceutical, chemical, biotechnology and medical device companies. Some of these companies were launched on the basis of his patent licenses. From 1995 to 2002 he served as a member of the United States Food and Drug Administration's SCIENCE Board, the FDA's highest advisory board and from 1999 to 2002 he acted as Chairman.

Bob Langer's work is at the interface of biotechnology and materials science. A major focus is the study and development of polymers to deliver drugs, particularly genetically engineered proteins, DNA and RNAi, continuously at controlled rates for prolonged periods of time. Work is in progress in the following areas:



- *Mechanism of release from polymeric dds with concomitant microstructural analysis and mathematical modeling.*
- *Studying applications of these systems including the development of effective long-term delivery systems for insulin, anti-cancer drugs, growth factors, gene therapy agents and vaccines.*
- *Controlled release systems that can be magnetically, ultrasonically, or enzymatically triggered to increase release rates.*
- *Synthesizing new biodegradable polymeric delivery systems which will ultimately be absorbed by the body.*
- *Creating new approaches for delivering drugs such as proteins and genes across complex barriers in the body such as the blood-brain barrier, the intestine, the lung and the skin.*
- *Researching new ways to create tissue and organs including creating new polymer systems for tissue engineering.*
- *Stem cell research including controlling growth and differentiation.*
- *Creating new biomaterials with shape memory or surface switching properties.*
- *Angiogenesis inhibition*

Prof. Langer has received nearly 150 major awards. In 2002, he received the *Charles Stark Draper Prize*, considered the equivalent of the Nobel Prize for engineers and the world's most prestigious engineering prize, from the National Academy of Engineering. He is also the only engineer to receive the *Gairdner Foundation International Award*; 68 recipients of this award have subsequently received a Nobel Prize. Among numerous other awards Langer has received are the *Dickson Prize for Science* (2002), *Heinz Award for Technology, Economy and Employment* (2003), the *Harvey Prize* (2003), the *John Fritz Award* (2003) (given previously to inventors such as Thomas Edison and Orville Wright), the *General Motors Kettering Prize for Cancer Research* (2004), the *Dan David Prize in Materials Science* (2005) and the *Albany Medical Center Prize in Medicine and Biomedical Research* (2005), the largest prize in the U.S. for medical research. In 2006, he was inducted into the National Inventors Hall of Fame. In 1998, he received the *Lemelson-MIT prize*, the world's largest prize for invention for being "one of history's most prolific inventors in medicine."

In 1989 Bob Langer was elected to the Institute of Medicine of the National Academy of Sciences, and in 1992 he was elected to both the National Academy of Engineering and to the National Academy of Sciences. He is one of very few people ever elected to all three United States National Academies and the youngest in history (at age 43) to ever receive this distinction.

Forbes Magazine (1999) and Bio World (1990) have named Langer as one of the 25 most important individuals in biotechnology in the world. Discover Magazine (2002) named him as one of the 20 most important people in this area. Forbes Magazine (2002) selected Langer as one of the 15 innovators world wide who will reinvent our future. Time Magazine and CNN (2001) named Langer as one of the 100 most important people in America and one of the 18 top people in science or medicine in America. Parade Magazine (2004) selected Langer as one of 6 "Heroes whose research may save your life." He has served, at various times, on 15 boards of directors and 30 Scientific Advisory Boards of such companies as Wyeth, Alkermes, Mitsubishi Pharmaceuticals, Warner-Lambert, and Momenta Pharmaceuticals. Prof. Langer has received honorary doctorates from Yale University, the ETH (Switzerland), the Technion (Israel), the Hebrew University of Jerusalem (Israel), the Universite Catholique de Louvain (Belgium), the University of Liverpool (England), the University of Nottingham (England), Albany Medical College, the Pennsylvania State University, Northwestern University and Uppsala University (Sweden). He received his Bachelor's Degree from Cornell University in 1970 and his Sc.D. from the Massachusetts Institute of Technology in 1974, both in Chemical Engineering.

Source: [Langer Lab website](#)

TRENDS IN OCULAR DRUG DELIVERY WITH FOCUS ON POSTERIOR EYE

by Dr. Stefan Bracht, Pharmaceutical Development ED&DDS, [Bayer Schering Pharma AG](#), Müllerstr. 178, 13353 Berlin

Introduction

Today drug delivery to the eye can vary from relatively simple topical eye drops up to intravitreal implants. Based on recent progress with numerous delivery routes and concepts it turns out that the eye is an even more complex organ than already known from the anatomy text books: numerous liquid compartments, tissues, membranes, and vasculature provide a fascinating environment for drug diffusion, absorption, and clearance.

Current interest in ocular delivery is very much driven by new drugs which could be used to treat various diseases mainly of the posterior eye if they can be delivered locally and be made available for long term drug release.

The anterior segment consists of cornea, conjunctiva, iris, ciliary body and the lens with its zonules. The posterior eye mainly comprises posterior chamber, choroid, sclera, retina and the vitreous body.

Overview of ocular drug delivery

Topical delivery is the most convenient method for the anterior segment. The anterior can best be reached with eye drops, gels, creams, ointments or subconjunctival injections. It is non invasive, first-pass effect can be circumvented, and the drug is targeted to the anterior part of the eye. However, topical delivery is affected by e.g. rapid drug clearance into the lacrimal duct and low permeability of the cornea to many drugs. This often results in absorbed drug fractions of less than 5% dose and can go along with unwanted systemic side effects caused by the excess dose that is cleared into the upper respiratory system and absorbed locally. Many concepts exist to prolong local drug residence time by e.g. mucoadhesive micro or nano particles. Enhancers can be employed to lower the corneal barrier function. The cornea is a very effective barrier specifically to hydrophilic drugs but also to lipophilic compounds. Part of this barrier appears very familiar to experts in transdermal and transmucosal delivery and similar concepts of permeation enhancement are applied – keeping in mind the limitations by the high potential of local eye irritation. Medicated contact lenses, drug loaded collagen shields or in situ gel forming systems can also be employed for sustained release to the cornea and anterior conjunctiva.

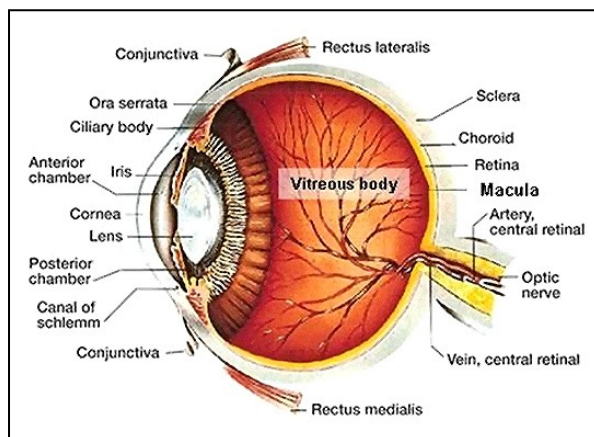


Fig 1: Anatomy of the human eye in detail.

Even ocular iontophoresis and electroporation are investigated to overcome the corneal barrier which have been vastly explored in transdermal drug delivery over more than 2 decades. Current results are also similar in that major success is reported for polar compounds and macromolecules but local current to be applied is typically 1-2 mA/cm² at maximum when local irritation or side effects are to be avoided. Gel type electrodes seem to be better tolerated than metal electrodes. Iontophoretic equipment can hardly be miniaturized to the degree of wearing an integrated device at or on the eye so that indoor treatment is required.

Subconjunctival injections are less popular for drug delivery to the anterior eye due to lower tolerability and higher risk of local side effects specifically in inflamed eyes.

Many achievements can be reported but drug delivery to the anterior is not in the focus of this article.

Posterior eye and retina

A strong medical need to access the posterior eye by other than systemic routes arose from the cytomegalovirus retinitis associated with AIDS and resulted in the development of the Vitrasert intravitreal implant which was registered in 1996 as a pioneering drug delivery system in this field.

In recent years two other diseases have been the main driving force: Age related macula degeneration (AMD) and diabetic retinopathy (DRP) are both associated – among other pathophysiological phenomena – with neovascularisation which is a target in solid tumor therapies as well. Antiangiogenesis has made much progress especially about vasoendothelial growth factor (VEGF) and numerous drugs in development to directly or indirectly inhibit VEGF.

Delivery to the posterior eye and retina is of much greater challenge than the anterior: Topical drug delivery today comprises various periocular routes like subconjunctival, retrobulbar, peribulbar injections and implants up to the most invasive methods of direct intravitreal injection or implantation.

Many inflammatory diseases of the posterior are still treated systemically with steroids or antibiotics given that these compounds are good permeants to the blood ocular barrier. This latter barrier is shielding the retina by the blood retina barrier (BRB) which is reported to be similarly effective as the blood brain barrier (BBB). The choroid is highly vascularized with permeable capillaries but other barrier mechanisms like retinal pigment epithelial cells (RPE) still limit drug delivery from choroidal capillaries to the vitreous and the retina.

Intravitreal drug delivery and implants can best overcome this issue but are associated with complications and ocular maladies like retinal detachment at levels which is reported in the range of 10 %. Recent developments on implants have strived to maximize the application period in order to minimize invasive surgery over time, e.g. Retisert™ as compared to Vitrasert™.

Biodegradable or bioerodable implants are limited on one hand by the typical release kinetics of initial burst effect followed by relatively linear release and ending with another burst release upon final disintegration of the implant. On the other hand the erosion process had to be slowed down considerably to meet target profiles of 6 months application period or greater. Since most biodegradable polymers are poly acids or poly anhydrides (see section on polymers below) it is important to always consider the acidic pH-shift during biodegradation and potentially employ buffering concepts in order to minimize pH-related irritation.

Many successful developments have been made to minimize and control all of these effects and application periods have been changed from days and weeks to the range of 3 to 6 months which appears to be the current maximum.

Non degradable implants of the reservoir type can be used to better control drug release and offer more flexibility to the formulator in the field of polymers, composition and release control mechanisms. Drug payload can mostly be higher compared to biodegradable systems due to the higher amount of polymer matrix usually required for the latter. Drug release can be slowed down in these systems to currently reach application periods of 3 years potentially reaching a maximum of 5 years. These systems have to be surface shielded with biocompatible polymers like silicones and whenever the surface is partly covered with other polymers – e.g. drug release controlling membranes and orifices or adhesive means – care is recommended to prevent adherence of cells or tissues to these sections. Such mechanisms could affect long-term drug release and hamper implant removability.

Intravitreal implants require cuts into the sclera/choroid of currently 3-6 mm in length – smaller devices require shorter cuts but are feasible only for highly potent drugs with total payload of the device in the low milligram or even sub-milligram range. Particulate reservoir formulations have been developed that can be injected with a needle to minimize the invasive procedure. The smaller the particles the shorter the drug release will usually be due to the increased surface area. The vitreous is a liquid reported to have 3-4 times higher viscosity than water which means that sedimentation in the vitreous can still occur. Nano particles do not show this effect due to Brownian motion and at an average diameter of about 50 nm they do not interfere with light in the VIS range. On the other hand sustained release from nano particles is much more challenging than from micro particles and can hardly be achieved for more than days or a couple of weeks based on current technical status.

The composition of the vitreous is reported to change in the elderly mostly by reduced viscosity and loss of homogeneity both to be taken into account for particulate or emulsion type intravitreal formulations.

The strictly outward flow of liquids from the vitreous to the aqueous means that drugs are not typically distributed homogeneously in the vitreous and potentially effective concentrations in the retina can still not be reached from here.

Due to the highly invasive nature of intravitreal application the transscleral route currently gains much attention. Interestingly the sclera is reported to be well permeable to low molecular drugs up to 300 Da – hydrophilic compounds permeate more readily than lipophilic compounds - and even macromolecules of some 70 – 100 kDa were found to sufficiently permeate this barrier. When exploring this new route researchers found out that despite high scleral permeability only a small fraction of the drug applied to the sclera (episclerally or intrasclerally) reaches the vitreous. This has been attributed to both retrograde clearance into conjunctival vasculature and also episcleral veins may play a role.

On the way from sclera to vitreous the choroidal vasculature can contribute to drug clearance and also melanin binding has been identified to potentially limit the availability of drugs binding to this molecule which can be found in high amounts in human choroid.

Consequently, efforts have been made to prolong episcleral or intrascleral residence time of the drug and not to release drug from there in opposite direction to the conjunctiva. The sclera is reported to vary in thickness from about 0.4 at the equator up to 1.0 mm at the optic nerve meaning that results from transscleral drug delivery can vary by location on the eye ball.

The project **Retane**™ by Alcon Labs is designed as a juxtасcleral posterior depot injection to treat choroidal neovascularization. Filings have been made in the U.S. and the EU. In 2006, the EU filing was withdrawn, after the EMEA had concerns about insufficient clinical efficacy. Whether these efficacy issues might be related to suboptimal drug targeting is not known and just speculation.

Transscleral drug delivery seems to be one of the most attractive fields of formulation development in ocular drug delivery at present since it is clearly not yet fully explored.

In silico and in vitro models have been developed to facilitate better understanding of ocular drug delivery pathways – scleral membrane permeation is among these in vitro methods. The in vitro results have to be interpreted carefully since sclera appears to be quite permeable while the vascular clearance is in the focus of interest which is usually not reflected by the model.

Animal models might be more relevant but again the fact that human and rabbit scleral permeability are comparable while bovine sclera is reported to be 5-10 times more permeable will not tell the full story.

Transscleral drug delivery is minimally invasive and will be an interesting field to watch for the near future.

A comprehensive overview of pharmacokinetic modelling options can be found in further reading [3].

A word on polymers

This section is to provide the reader with information on polymers currently approved or at least under clinical investigation since these will be easier to develop or register in the industrial development process. For abbreviations reference is made to further reading [4].

Among non-biodegradable polymers PVA, EVA, and silicones are in use as hydrophilic reservoir or membrane materials. Compared to the other two groups, PVA is not as frequently used in drug delivery systems. Sometimes cross-linked PVA is used to allow swelling but avoid dissolution. Cross-linkers should be evaluated carefully since they can be a source of toxicological concerns. Silicones are known to be highly permeable to low molecular weight lipophilic drugs. In case of hydrophilic drugs, salts and high molecular weight (>500-1000 Da) they can be employed as barrier polymer in contrast to what they are known for in other fields.

The field of erodable/biodegradable polymers is quite large and basically known to drug delivery experts. PLA, PGA, PLGA (e.g. Surodex[®]) are familiar abbreviations of polymers used to control (prolong) the degradation time of implants and to also deal with (slow down) the acidic pH-shift upon hydrolytic cleavage. PCL is a more hydrophobic material to be mentioned in this context. PCPP has been reported to enable extremely long degradation times of 3 years and greater.

Poly-ortho-esters (POE) are reported in classes I-IV of which III and IV are in clinical ocular use. The sometimes gel-like state of the material can ease the incorporation of drugs and also facilitate implantation with needles. pH-shift upon degradation and degradation times of typically weeks up to 3-6 months at maximum appear to be the remaining hurdles.

Industrial perspective and Summary

The focus of this section is on implantable systems. The most crucial need in this field is to lower the application frequency in the field of chronic ocular diseases, specifically with posterior drug delivery. Biodegradable implants exclude the need for removal but increase the risk of toxicological issues associated with degradation products. Non biodegradable implants offer more flexibility to control especially long-term drug release and to avoid initial or final burst effects. An important differentiator can also be the drug payload to be incorporated: 20-30 mg drug load can be seen as a realistic maximum for non degradable ocular implants while 5 to 10 times less drug may be feasible in degradable/erodible systems which by nature employ a higher fraction of the implant weight for polymers and excipients.

Much work is reported on permeability of various ocular membranes and tissues. When developing long-term implantable systems it should be kept in mind that drug release from the system is the predominant step governing the total PK since no ocular tissue appears to be suited to slow down drug permeation in the range of months or years (with many transdermal systems the stratum corneum acts as a suitable barrier membrane for 1-7 days). Thus, an in vitro drug release model is a valuable tool to investigate the ability of the systems long-term properties. Standardized and/or accelerated test models are still needed.

The next step of in vitro testing is to use permeation models which can be found in the literature and can be used to test specific permeability of e.g. sclera or the risk of melanin binding.

Tissues from rabbit or bovine eye are more accessible than human eye from an industrial perspective and more work is needed on representative models like they have been discussed and improved for many years in transdermal drug delivery.

Ocular drug delivery can be monitored non invasively in vivo by magnetic resonance imaging (MRI) when e.g. gadolinium labelled marker molecules are used like Gd-DTPA.

The field of ocular implants is today occupied by some highly specialized companies like among others Alcon, Allergan, Bausch and Lomb, or pSivida of which the latter is strongly co-operating with Pfizer. Novartis is also active in this field. Looking into commercial databases (e.g. www.pharmacircle.com) and also looking into the recommended readings of this article, a number of enterprises can be found with proprietary technologies.

The driving force for future developments should come from mid size and big Pharma companies which have promising drug candidates in their pipelines to treat diseases of the posterior eye.

The current status of approved drugs and drugs in development can be found in further reading [2].

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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. [Read more...](#)

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