ITI Life Sciences

Drug Delivery Foresighting Report

March 2008

Executive Summary

- Advances in drug delivery have revolutionised the human healthcare sector by providing better ways to deliver medicines to the body. Once ground-breaking advances, technologies such as metered-dose inhalers, transdermal patches and drug-eluting stents have now become standard treatment
- Indeed, although these are generally mature markets, there are **pockets of innovation** within many of the older areas that are leading to the generation of new intellectual property (IP) and technology platforms
  - A good example of this is transdermal patches, where advances in active delivery mechanisms have introduced the possibility of delivering macromolecules, which was impossible with traditional passive patches
- Selecting the right method of delivery of a pharmaceutical product is vital to its success once it reaches the market. In order to generate a **competitive edge** big pharma is actively seeking access to new technologies. This means there is a healthy market for companies seeking to out-license or sell their latest technology – providing it is supported by proof of concept studies
- Due to the breadth of the drug delivery area, we selected four of the most innovative areas within drug delivery for foresighting: **transdermal**, **microcapsules**, **nanoparticles** and **ocular delivery**

Advances in drug delivery have shaped the modern healthcare world – but there is still a need for next-generation innovative technologies

Executive Summary, cont

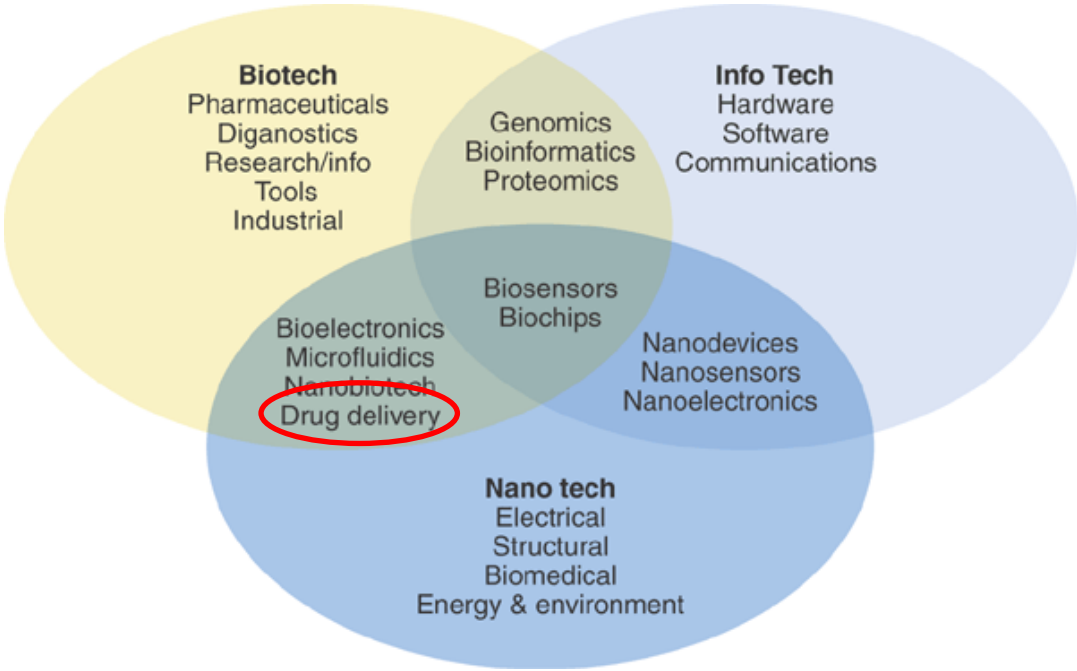
- Within the **transdermal** area we found that advances in active delivery of compounds through the skin has opened the possibility of delivering proteins to the body using this technology, with insulin being one of the first compounds under investigation
- **Microcapsules** are commonly used in a wide variety of non-life science industries but recent work from ARS has suggested a new application for this technology in the area of drug delivery. Many questions remain over this technology, but the potential upside is significant for the industry
- **Nanoparticles** have been around for a number of years now but have struggled to reach their full potential. Advances in this area have raised the possibility of nanoparticles being part of the answer to getting drugs across the more inaccessible and impermeable barriers in the body
- **Ocular delivery** is at an interesting stage in its development, with the recent adoption of more invasive delivery methods, such as intra-vitreal injections and device implantation. This has enabled the delivery of biologics to the eye for a number of serious conditions with high unmet clinical need. Significant opportunity exists for the non-invasive delivery of biologicals into the eye

Drug delivery is an active area for the development and application of new technology

Contents

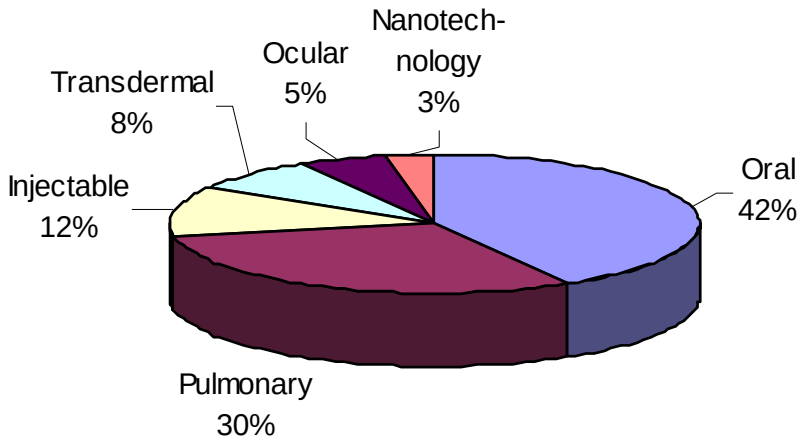
Scope

- Drug delivery includes a very broad range of technologies. For the purposes of this report we have defined it as anything that is associated with *improving the delivery, performance or safety of a therapeutic product*, but excluding devices which contain no therapeutic as part of their effect



Market Size

- The global drug delivery market is dominated by drugs delivered through the oral and pulmonary route. Indeed for many pharma companies oral is the 'holy grail' of therapeutic administration. Many innovative delivery vehicles have been developed to provide greater control over the delivery of oral compounds
- While the pulmonary area is now fairly mature, much has been invested into trying to develop inhaled insulin. Unfortunately the first commercialised product, Pfizer's Exubera, was eventually pulled from the market following a very disappointing performance
- Many compounds, particularly biologicals, are too large to be formulated for oral administration and must be injected directly into the body. However, with the emergence of novel transdermal patches and nanotechnology techniques, these barriers are now being overcome

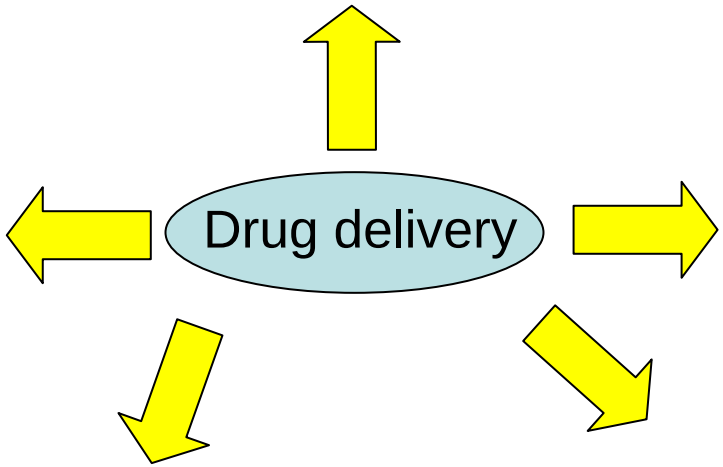


The global drug delivery market was worth an estimated $80bn in 2006 and was dominated by the oral and pulmonary sectors

Benefits of Drug Delivery

Increased compliance: through improved administration e.g. injectable depot formulation

Enhanced efficacy: through optimising the therapeutic dose delivered e.g. oral sustained-released systems



Improved convenience: through greater patient freedom e.g. transdermal patches

Improved safety: through reducing side effects of systemic delivery e.g. eye drops

Indication extensions: through use of novel delivery mechanisms for established drugs e.g. intravitreal injections

Market Dynamics

- A number of factors has led to an increased focus on drug delivery as an effective life-cycle management strategy

Inhibitors

Costly R&D investment

Technology limitations

Tangible therapeutic improvements

Drug Delivery

Drivers

Faster generic penetration

Innovative new technology

Patent expiries of blockbusters

Thinner R&D pipelines

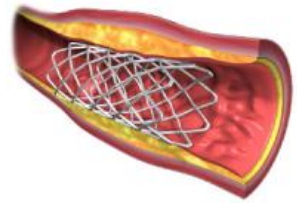
Greater acceptance of generics

Inconvenient administration of biologics

Increasing emphasis on life-cycle management

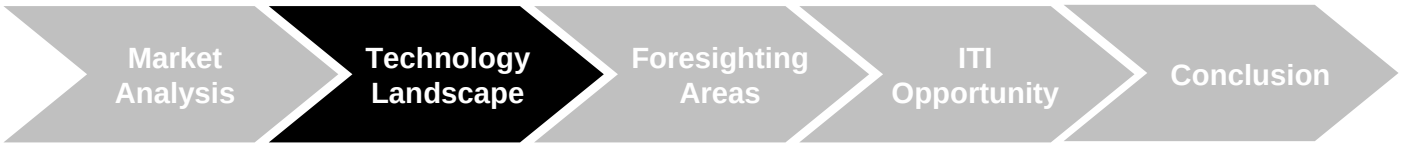
Example of Disruptive Drug Delivery

- A good example of a drug delivery technology that has disrupted the established market place is the arrival of **drug-eluting stents** (DES) in 2002 for the treatment of coronary artery disease. The build up of plaque on coronary arteries (atherosclerosis) can eventually lead to partial or complete closure of these vessels and result in infarction to the surrounding tissue
- Interventional cardiologists have developed various techniques to re-supply blood to the heart, one of which is to unblock the thrombus and implant a stent – a wire metal mesh tube that is used to prop open an artery, now referred to as bare metal stents (BMS)
- In 2002, Cordis, a subsidiary of J&J, launched its **Cypher stent** in Europe. Cypher is coated in sirolimus, an immunosuppressant that Wyeth had previously launched as Rapamune for transplant indications. Shortly after the paclitaxel-eluting Taxus stent was launched by Boston Scientific in Europe
- Clinical data demonstrated significant **reductions in restenosis** and **revascularisation** procedures compared to BMS, and DES quickly became the stent of choice among many cardiologists. Only a few years after the launch of the first products, rapid adoption of DES led to the market reaching $2.8bn in 2006
- While recent studies have questioned the benefits of DES over BMS and/or medical therapy there is no doubt that this technology has had a dramatic impact on the medical device industry



The Cypher stent

Contents



- Scope
- Size
- Benefits
- Dynamics
- Stent Example

- Segmentation
- Deal Flow
- Attractiveness
- Scale

- Transdermal
- Microcapsules
- Nanoparticles
- Ocular delivery

- Future Trends
- Scottish Fit

Segmentation by Route of Delivery

Oral

- Controlled/sustained release
- Delayed release & modification
- Fast dissolving
- Taste masking
- Pulsatile release
- Microemulsion
- Macromolecular delivery
- Hydrophobic drugs
- Hydrocapsules

Injectable

- Needle-free
- Implantable
- Sustained-release
- Targeted injection
- Pen injection
- Nanotechnology
- Microsphere technology
- Microchip technology

Transdermal

- Membrane-controlled system
- Adhesion diffusion-type system
- Matrix diffusion
- Microreservoir dissolution-controlled
- Electrotransport drug delivery
- Iontophoresis & sonophoresis
- Transmucosal drug delivery
- Ultrasound

Ocular

- Intravitreal
- Lenses
- Eye drops
- Transscleral
- Nanoparticles
- Iontophoresis

Pulmonary

- Metered dose inhaler
- Dry powder formulations
- Nebulizer delivery formulations
- Liquid formulations
- Nanospheres
- Intranasal delivery technology
- Nano & micro particulate systems
- Prodrug drug delivery
- Electrohydrodynamic aerosol delivery
- Oxygen delivery
- Crystallisation technology

Bullets list a selection of the types of technologies used in the various routes of administration

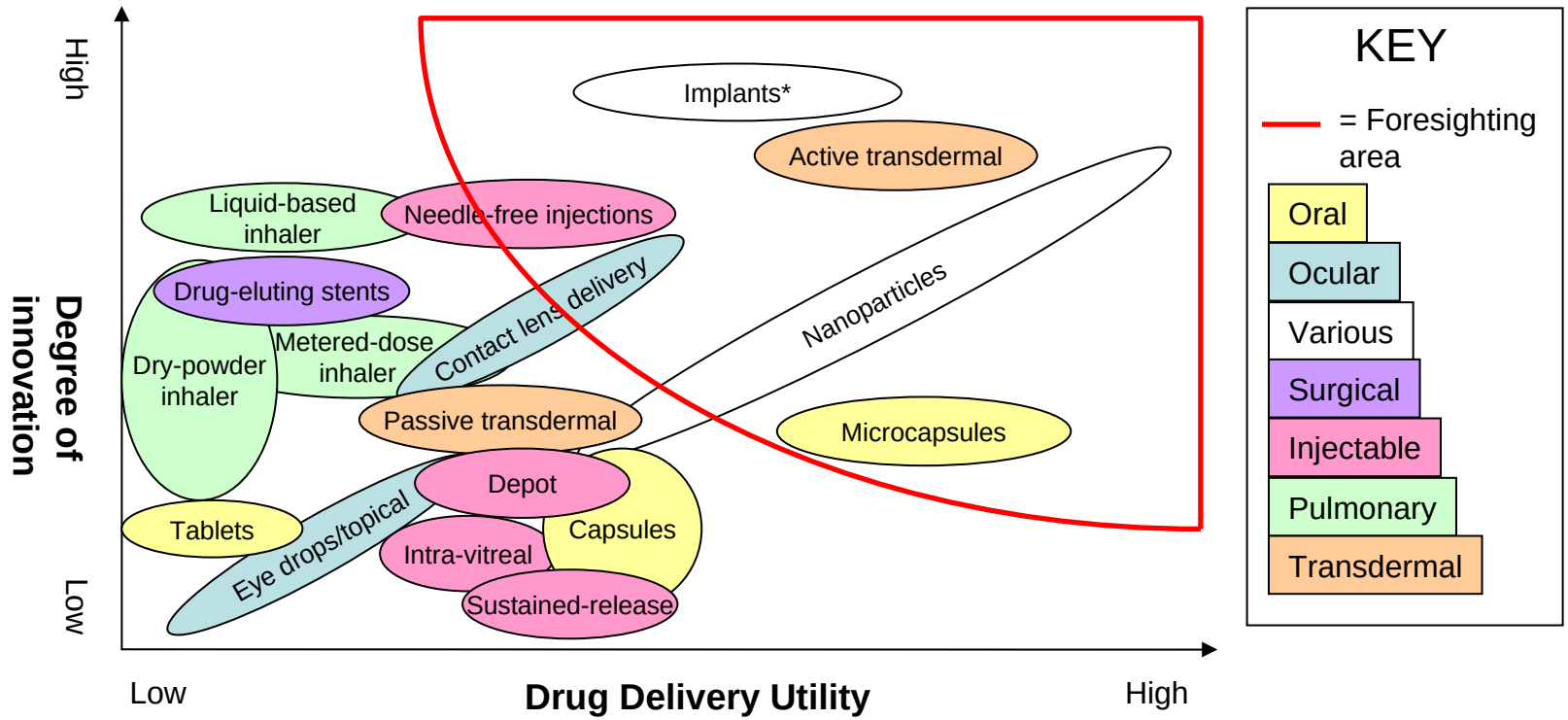
Drug Delivery Deals

- The total number of drug delivery deals has increased steadily in recent years, exceeding 330 in 2007, approximately 12% of all pharma deals
- This increase has been driven by a sharp rise in the number of **drug delivery licensing** deals between biotech and big pharma. The number of deals reached 153 in 2007, up from 63 in 1997
- The number of **R&D collaborations** and **co-development** deals has remained relatively steady over recent years, within the 40-60 deals per year bracket. **M&A** deals involving drug delivery companies have increased steadily in recent years, reaching 27 in 2007, up from six in 2003
- Significant licensing and acquisitions drug delivery deals include:
  - Wyeth acquired Haptogen in October 2007
  - Roche licensed Halozyme Therapeutics' drug delivery technology, Enhanze, in 2006
  - Pfizer acquired PowderMed and acquired full rights to Exubera from Sanofi-Aventis in 2006
  - Endo Pharmaceuticals acquires RxKinetix - reformulates compounds for the treatment of oral mucositis in 2006
  - J&J acquired Conor Medsystems, a cardiovascular device company, for $1.4bn in 2006

The number of drug delivery deals is continuing to rise, driven by licensing and M&A deals

Technology Attractiveness

- Drug delivery technologies can be classified by both their relative degree of innovation and utility. Innovation describes how complex the delivery technology is, while utility describes the usefulness of the delivery device – both in terms of the range of compounds that can be delivered by this mechanism, as well as the range of possible delivery routes:

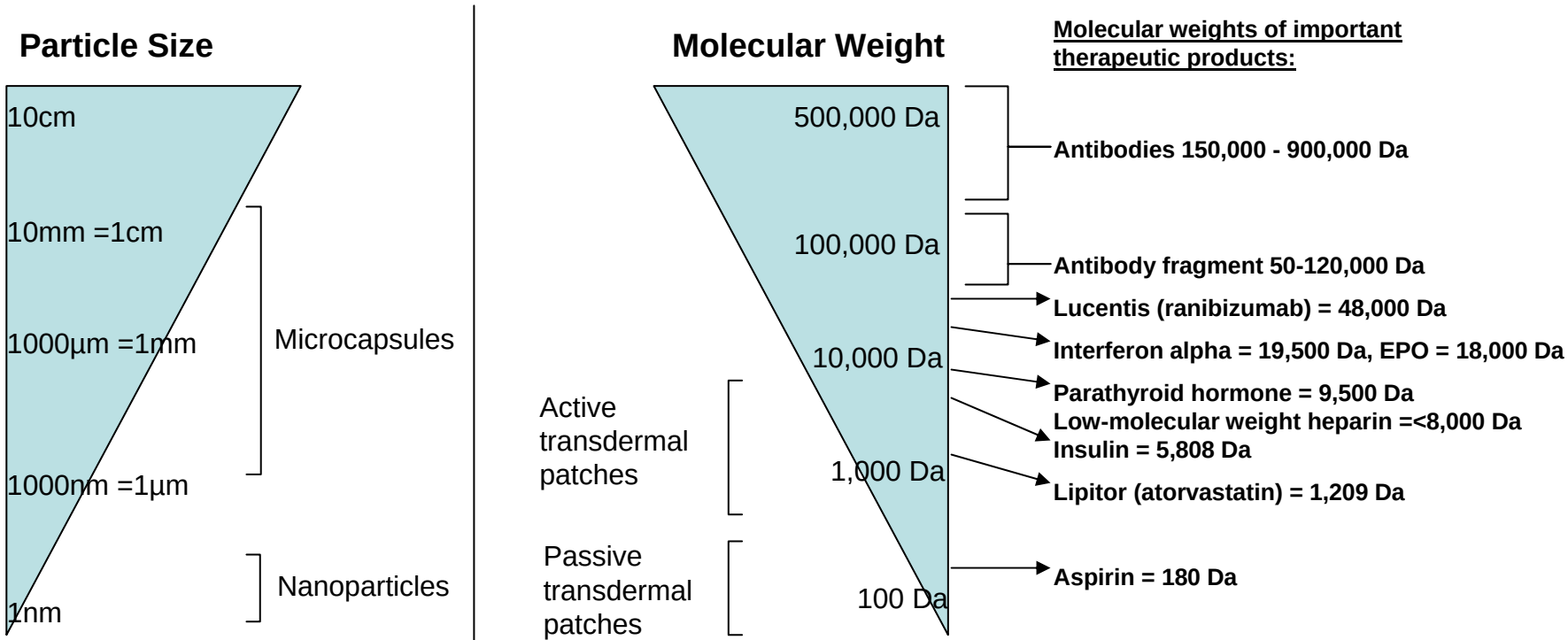


Technologies that are both innovative and have a high degree of utility are ideal for the delivery of therapeutic compounds

Two case studies are highlighted in this report, for analysis of other therapeutic implants, see the Minimally Invasive Medical Devices E-Scan

Size and weight

- This foresighting report focuses on various levels of scale within drug delivery:



Drug delivery technologies are grounded on an understanding of molecular weight and particle size

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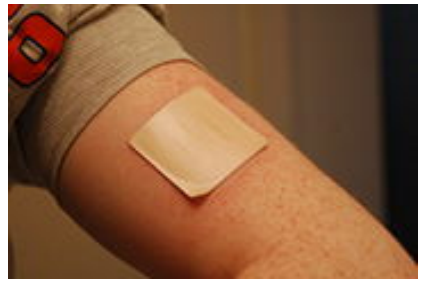
Foresighting Areas

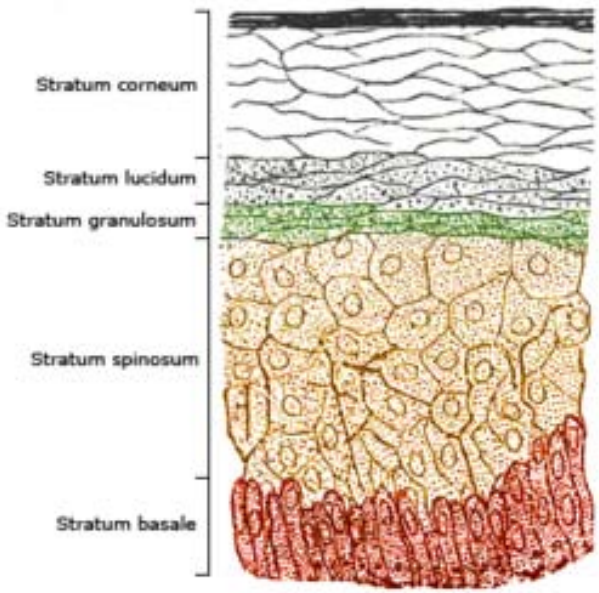
- **Transdermal**
- Microcapsules
- Nanoparticles
- Ocular Delivery

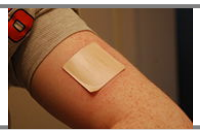
- Background
- Benefits
- Challenges
- Novel Approaches
- IP Landscape
- Research Activity
- Leading Companies
- Case studies x3



Background

- Transdermal drug delivery offers controlled release of a drug into the patient
- It enables a steady blood-level profile, resulting in reduced systemic side effects and potential for improved efficacy over other dosage forms
- Transdermal patches are user-friendly, convenient, painless, and offer multi-day dosing
- Since 1981, the FDA has approved more than 35 transdermal patch products, spanning 13 molecules
- However, many compounds cannot be absorbed through the skin or, if they are, are only absorbed in very small quantities, meaning transdermal delivery has not been a possibility
- The major barrier is the stratum corneum – the layer of dead skin 10-20 micrometers thick

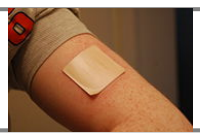




Transdermal patches have been available for many years, but have been restricted to compounds small enough to cross the stratum corneum

Benefits of Transdermal Delivery

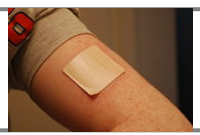
- Key benefits:
  - Non-invasive
  - Painless
  - More convenient
  - Avoids first pass metabolism in liver
  - Not affected by food intake or gastric acidity
  - Can immediately withdraw treatment
  - Controlled release of drug
  - Suitable for drugs with very short half-life, narrow therapeutic window and poor oral absorption
- New technologies can deliver macromolecules through the skin, could offer new approaches in:
  - Diabetes
  - Vaccination
  - CNS diseases



The next generation of transdermal devices bring the advantages of traditional patches to a wider spectrum of compounds

Challenges of Transdermal Delivery

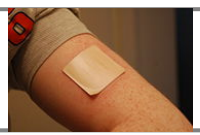
- The skin is a natural barrier that must be crossed without its composition being compromised. This can be done by using chemical penetration enhancers – surfactants, fatty acids and fatty esters can alter the structure of the stratum corneum
  - But they are not selective for intercellular lipids and also affect membrane lipids of epidermal cells and induce irritation
- The ultimate objective is to increase the spectrum of drugs that can be delivered through the skin while also eliminating the risk of damage and contamination of the skin
- Another aim is to increase the speed of delivery through the transdermal route, which depends on the:
  - Size of the molecule
  - Rate of absorption
  - Potential for skin damage, pain or irritation



The main challenge is to overcome the stratum corneum by increasing the permeability without significantly changing barrier function

Novel Approaches

- A range of techniques has evolved aimed at increasing the skin's permeability without irreversibly changing barrier function
- Chemical penetration enhancers:
  - **Surfactants –** fatty acids, fatty esters alter the structure of the stratum corneum. But they are not selective for intercellular lipids and also affect membrane lipids of epidermal cells and induce irritation
- Active transport techniques:
  - **Iontophoresis** – electrically transports molecules across the skin e.g. Active Patch System (Vyteris)
  - **Heat** – e.g. PassPort (Altea)
  - **Ultrasound** - e.g. Encapsulation System's U-strip insulin patch
- Mechanical techniques:
  - **Poration** – high-frequency pulses of energy to create pores in the stratum corneum e.g. MTS (3M)
  - **Laser** – e.g. Laser Assisted Drug (LAD) delivery, developed by Norwood Abbey

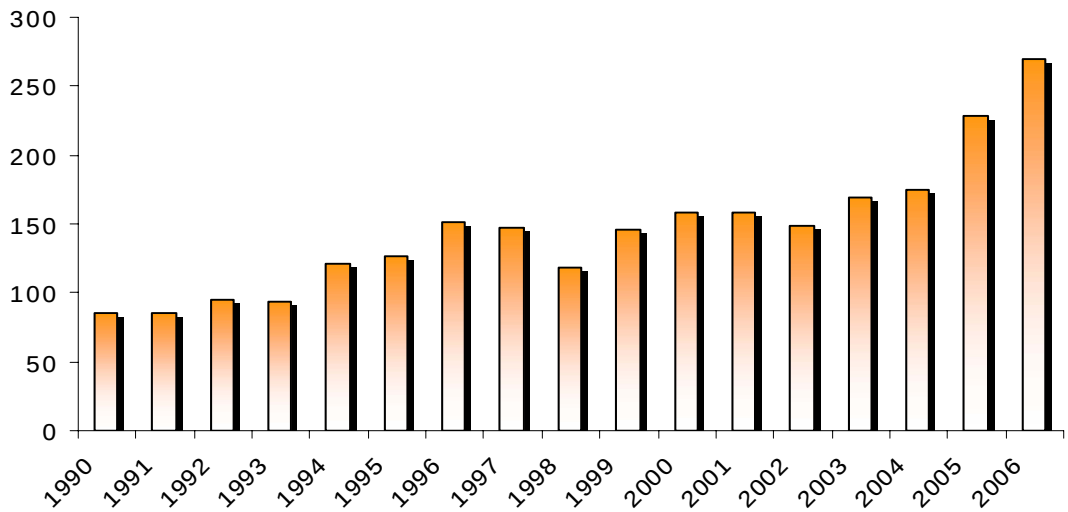


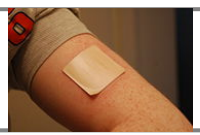
Using these methods can dramatically increase the number of compounds that can be delivered transdermally

IP Landscape

- There has been a steady increase in the patent activity involving transdermal patches. A sharp increase in recent years reflects the development of new technologies using active transport mechanisms
- Key words used for patent search were: transdermal or percutaneous or transcutaneous or microneedle or iontophore

Number of patents filed per year (1990-2006)

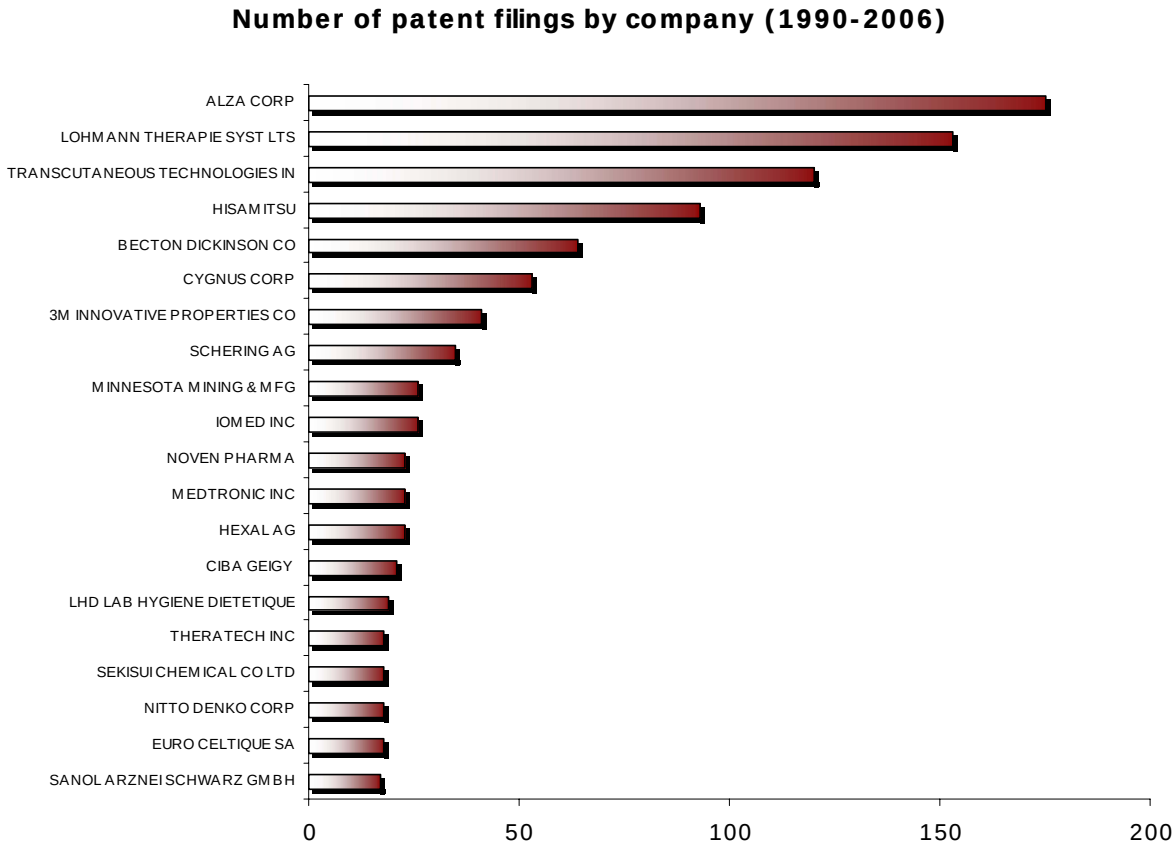




Transdermal drug delivery has been an active area for IP, particularly since 2004

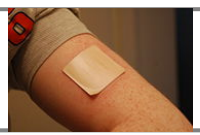
Research Activity

- Specialist technology companies are very active in this field, along with a number of research institutes. Underpinning its strong position in this market, Alza has been the most prolific in filing patents on transdermal patches, closely followed by the transdermal specialists Lohmann Therapie



Leading Companies

Company	Technology	Products	Comments
3M	Microstructured Transdermal System (MTS)	Minitran transdermal delivery system, Climara	
Altea	PassPort	Transdermal insulin patch	
Alza	D-TRANS, E-TRANS & Macroflux Transdermal Technology	Numerous patches are on the market using these technologies	A major innovator in this technology space
Aveva	Gel Matrix Adhesive, Crystal Reservoir Technology	Numerous patches are on the market	
Dermisonics	U-Strip Transdermal Drug Delivery System		
Encapsulation Systems	Ultrasonically Enhanced Transdermal Drug delivery System	U-Strip Insulin Patch (Phase II)	
Lavipharm	Transdermal Drug Delivery Systems, Solid Gel and Liquid Patch Technologies	Nitrong TTS, Fentadur, Trinipatch	Greek based small pharma
NuPathe	SmartRelief – iontophoresis patch	NP101 (migraine) Phase I	
OBJ	Active Patch – claim to deliver up to 200 kDa	Tetracaine (pilot study)	
Phosphagenics	TPM carrier gel. TPM-01 (small molecules), TPM-02 (peptides up to 30,000 Daltons)	Morphine, atropine, insulin, parathyroid hormone + other undisclosed peptides	Entered collaboration with Alza in November 2005
TheraJect	Drug & Vaccine Micro-Needle Array Transdermal Delivery System (DrugMAT & VaxMAT)	Influenza vaccine + others	
TransDermal Technologies	Transdermal Delivery System – able to deliver small peptides between 150-975 Daltons	Morphine, lidocaine, ibuprofen, acetominaphen, Hydroxyzine TDS, Testogen TDS	A liquid or semi-solid vehicle
Valeritas	h-Patch, e-Patch, Micro-Trans Microneedle Transdermal Delivery System	V-Go – Once-daily disposable insulin (awaiting launch)	
Vyteris	Active Patch System	LidoSite launched in 2007 but de-emphasised in February 2008	Now focussed on peptide delivery
Zosano Pharma	Macroflux transdermal patch technology	parathyroid hormone transdermal patch (Phase II)	Zosano was a J&J spin-out from Alza

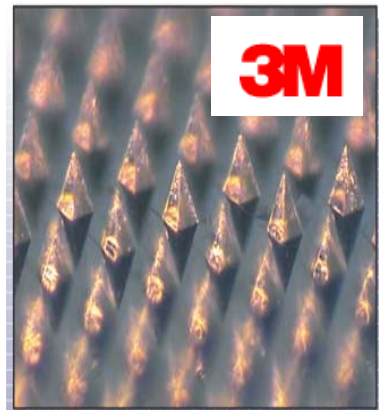


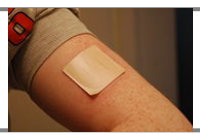
A selection of the leading companies in this space reveals a variety of technologies is used

RED = case studies

Case Study 1. 3M's MTS

- A promising poration technology for the delivery of biologics is microneedle-enhanced delivery
- These systems use an array of tiny needle-like structures to open pores in the stratum corneum and facilitate drug transport
- An example of this system, 3M's Microstructured Transdermal System (MTS), is shown here
  - The structures are small enough that they do not penetrate into the dermis and thus do not reach the nerve endings, so there is no sensation of pain
- The structures can be:
  - Solid (serving as a pretreatment prior to patch application),
  - Solid with drug coated directly on the outside of the needles, or
  - Hollow to facilitate fluidic transport through the needles and into the lower epidermis
- These systems have been reported to enhance greatly (up to 100,000 fold) the permeation of macromolecules through skin



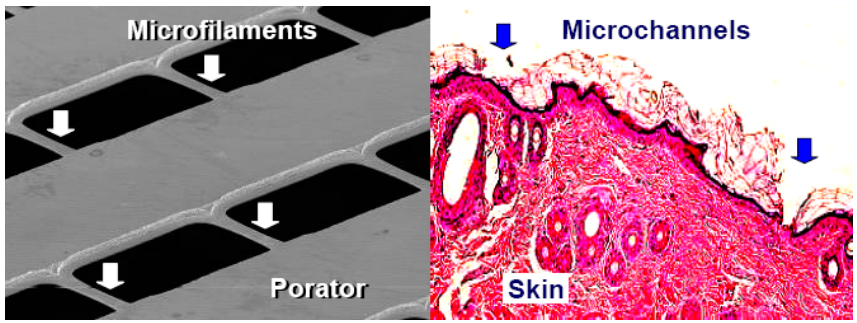


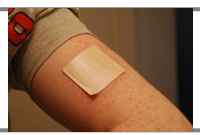
Microscopic needles create tiny pores in the stratum corneum allowing the delivery of biologics through the skin

Case Study 2. Altea's PassPort

- Altea Therapeutics is developing a transdermal patch with applications in delivering insulin, fentanyl citrate and a range of vaccines
- PassPort works by converting electrical energy supplied by an activator into thermal energy at the patch's microfilaments. This heat ablates the stratum corneum without any sensation of pain
- In May 2007 the company entered a research agreement with a major pharma player to develop a patch that delivers macromolecular carbohydrates for the treatment of coagulation disorders
  - They also announced that they had demonstrated the utility of its patch technology in delivering carbohydrate macromolecules in animal studies
- In October 2007 Altea released positive clinical results for a Phase I trial of its insulin transdermal patch in patients with Type I diabetes. The patch achieved therapeutic levels in patients equivalent to subcutaneous injection

ALTEA THERAPEUTICS



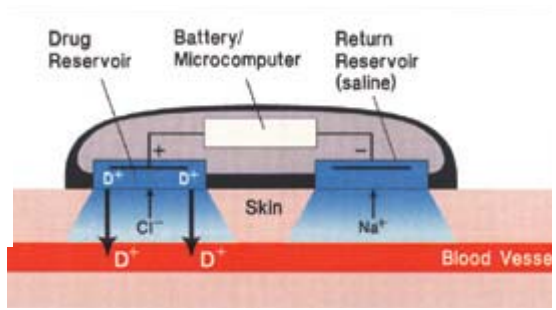


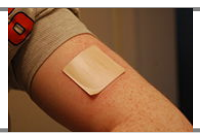
Altea's transdermal patch heats up microfilaments to create microchannels in the skin

Case Study 3. Vyteris' APS

- Iontophoresis describes the technique whereby electrically charged molecules are moved across the skin by repulsive electromotive force. Vyteris has demonstrated successful delivery of peptides up to 3.5kDa
- Drug flux is dependent on: molecular size & structure; charge; concentration; presence of competing ions or permeation enhancers in the formulation; size of patch and integrity of skin/patch interface
  - LidoSite (lidocaine) was launched in the US in August 2007 with B Braun. But Vyteris announced in February 2008 that the company was de-emphasising its promotion of LidoSite to focus on peptide delivery
- The Phase I trial was completed in a fertility peptide provided by Ferring in January 2008
- Also developing products for migraine, Parkinson's disease, women's health

vyteris





The Active Patch System uses iontophoresis to facilitate the movement of molecules across the skin

Foresighting Areas

- Transdermal
- **Microcapsules**
  - Background
  - Benefits
  - Leading companies
  - Case Study x2
  - Challenges
  - Applications
- Nanoparticles
- Ocular Delivery

Background

- Microcapsules are small particles or beads ranging in size from <1micron to several millimetres and which contain a wide variety of active ingredients
- There are three main types of microcapsule –
  - Aggregate or matrix (one substance uniformly distributed),
  - Mononuclear (a shell-core morphology) and
  - Polynuclear (more than one core enclosed within the shell)
- Hydrocapsules belong to this second category and are spherical droplets consisting of an inner core (encapsulate) and an outer (capsule) layer designed to encapsulate a solution inside a hardened outer shell
- Microcapsules also include encapsulation technologies where cells are enclosed in a capsule which is then delivered to a target organ

The development of hydrocapsules enables aqueous-based solutions to be delivered to target sites without being absorbed or degraded

Benefits of Microcapsules

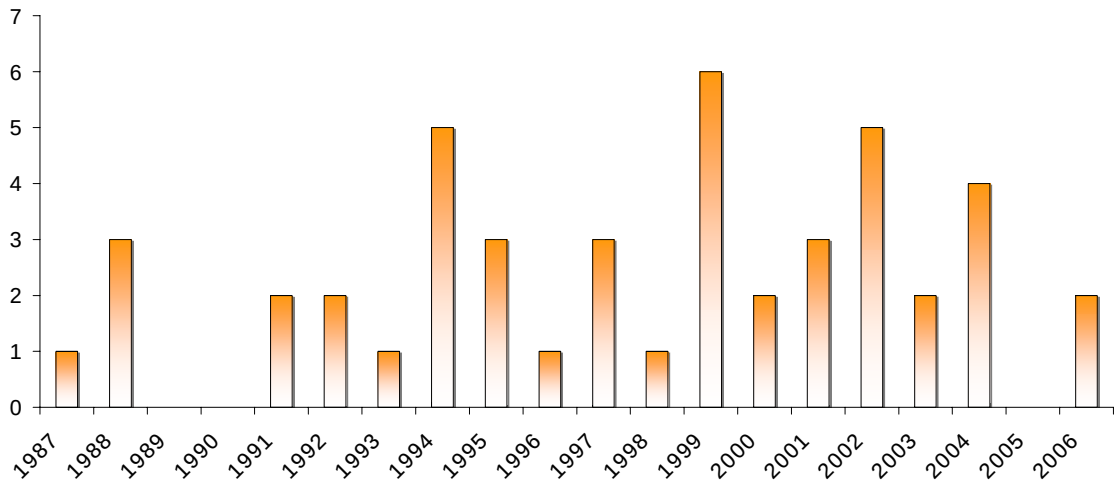
- Protecting sensitive materials from the environment prior to use
- Controlled and targeted delivery of encapsulate (compound, cells or organism)
- Enzyme and micro-organism immobilisation
- Preventing cleavage of precursor proteins once inside body
- Controlled, sustained or timed release of encapsulate
- Safe handling / transport of toxic substances
- Masking of odour or taste
- Ability to handle liquids as solids
- Self-life enhancement by preventing degradative reactions (oxydation, dehydration)

Microencapsulation provides a safe, convenient and effective means of delivering a biological substance to the target of choice

IP Landscape

- Microcapsules are widely used by the chemical, cosmetic and food industries. Hence, there are many patents covering their use as fragrance or ingredient packages
- However, relatively few patents cover the use of microcapsules as a vehicle of drug delivery, with no major players filing any patents since 2003. Also of note is that only two entities, the Japanese cosmetic company Lion Corp and the Southern Research Institute, filed more than one patent combining microcapsules with drug delivery
- Key words used for patent search were: microcapsule, hydrocapsule, mononuclear or polynuclear (and drug delivery)

Number of patents filed per year (1987-2006)



Microcapsules are a niche area of investigation in terms of using this technology to deliver therapeutic compounds to the body

Leading Companies

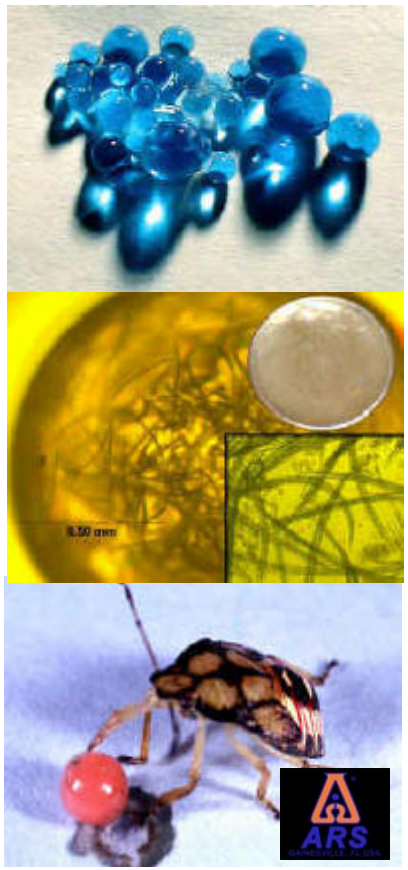
Company	Technology	Products	Comments
Analytical Research Systems (ARS)	Hydrocapsules - developed as a method for feeding beneficial insects		In discussions with pharma industry
Biotek	Microcoat biodegradable capsules	Depotrex depot naltrexone microcapsules	
BRACE GmbH	Microcapsules, microspheres, microencapsulation of aromes, antiallergic substances or phase change materials		No apparent expertise in healthcare products
Lipo Technologies	Lipocrystal, Lipocapsule, Lipoparticle, Liposphere	Various, including salicylic acid, tocopherol, menthol and triclosan	No apparent expertise in healthcare products
Medipol SA	Hynosphere	Natural biopolymers: alginate, chitosan, modified cellulose and heparin	
Nanocyte	Immediate Release Transdermal Drug Delivery Technology	Investigational	Uses a microscopic nanotube isolated from aquatic invertebrates
Ronald T Dodge Company	Matrix and liposomal encapsulation	Mainly a service provider with expertise in cosmetic and personal care industry	

RED = case study

Leading companies in the microcapsule area – but only one company is actively seeking opportunities in drug delivery

Case Study 1: ARS' Hydrocapsules

- Developed by Analytical Research Systems as a method for feeding beneficial insects and first used in a commercial application in 2000
- The inner core was originally designed to hold aqueous solutions but has applications across many different areas (nutrients, vitamins, drugs, vaccines, live organisms, viruses, tissues, cells, bacteria or fungi)
- In 2007 the company also began delivering entomopathogens (pathogens causing disease in insects) and semiochemicals (chemical signalling)
- Two mixtures are co-extruded from concentric nozzles under force – producing a bi-liquid stream containing two immiscible liquids
- The outer shell hardens and forms a sphere encapsulating the solution inside. The shell can also be designed to respond in different ways to its external environment:
  - Controlled release – gradual/rapid rupture of the shell or triggered release – by responding to changes in pH
- The inner encapsulate must have an aqueous content of between 10-100%. Capsule sizes are typically between 100microns to 2cm
  - "Several major players have showed interest in the past 10 months" Ara Manukian, CEO, ARS, January 2008



ARS have recently entered into discussions with major pharma reflecting the emerging interest in this area

Case Study 2: Encapsulation

Carnegie Mellon

- In November 2007, a research group at Carnegie Mellon University announced they had developed microcapsules capable of delivering genetically engineered adult neural stem cells into the brain where they then produce an essential enzyme
  - When such cells are re-implanted without a microcapsule, they elicit an inflammatory response, which causes them to differentiate into mature cells, rather than disperse throughout the brain
- The group, led by Prof Stefan Zappe and Dr Raymond Sekula were able to harvest adult neural cells, genetically engineer them, cause them to multiply outside the body, surgically implant the microcapsule in the brain and cause the cells to disperse once the outer casing of the microcapsule had been degraded
  - The degradation of the capsule is done by engineering the stem cells to produce a degrading enzyme
  - Once outside the capsule the cells migrate into the surrounding brain tissue and produce the enzyme of choice, iduronate-2-sulfatase, which is absent in patients with Hunter's syndrome
- Interestingly, the microcapsules can be instructed to allow the cells inside to proliferate, differentiate or migrate. The capsules can also control the extent of the migration
- The goal of the research is to genetically engineer neural cells from the patient, re-implant them and remotely control their actions in non-invasive ways

Researchers are using microcapsules to deliver genetically engineered stem cells to brain tissue

Microcapsule Innovation Barriers

- There are a number of challenges for the use of hydrocapsules in pharmaceutical applications:
  - Can the size of the capsules be standardised to acceptable limits?
  - Is the internal core sterile?
  - How will the manufacturing process affect biological products?
  - Will the process to harden the shell degrade any biological inside?
  - Will the active ingredients interact with the polymer shell?
- Moreover, the wide-spread use of encapsulated stem cells for therapeutic applications will require a better understanding of key questions such as:
  - How do the investigators control the size and thickness of the microcapsules?
  - How reliable is the degradation of the capsule by the cells?
  - How many cells migrate and how is this controlled?
  - How long do the cells survive for and continue to produce the chosen enzyme?

There remains a number of innovation challenges that need to be overcome before microcapsules can be widely used to deliver biological material to the body

Microcapsule Applications

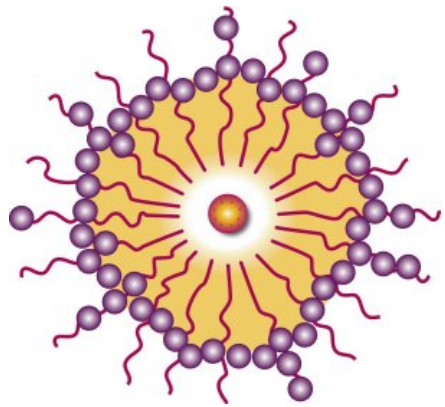
- As microcapsules are in the range of millimetres in diameter we believe the optimal route of delivery for any pharmaceutical applications will be oral
- Smaller particles could in theory be used in other delivery mechanisms but this will largely depend on whether the challenges mentioned previously, such as uniform particle size, can be demonstrated
- Microcapsules have broad application including potential use in the delivery of:
  - Attractant (bait) solutions, entomopathogenic nematodes, bacteria and fungi for pest control
  - Biological components such as animal blood products, brine shrimp eggs, water, animal and plant based protein solutions, oils and bacteria
  - pH sensitive polymer formulations for coating and delivery of entomopathagens (viruses and fungi)
  - Liquid nutritional / diet supplements for animals
  - Bacteria, fungi, viruses, cells, microbes, biological agents, vaccines, organisms
  - Bio-rational pesticides, water-proof traditional pesticides
  - Aqueous based pharmaceutical products – oral vaccines
  - Drug or nutrient delivery to aquatic animals

The range of potential encapsulates is vast – including bacteria, vaccines and live organisms

Foresighting Areas

- Transdermal
- Microcapsules
- **Nanoparticles**
- Ocular Delivery

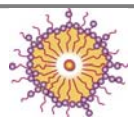
- Background
- Benefits
- IP Landscape
- Research Activity
- Leading Companies
- Case Study x2
- Challenges
- Application



Background

- The aim of nanoparticles in drug delivery is to improve drug uptake and specificity while also reducing side-effects. These aims can be achieved through drug encapsulation, reduced immune response and improved drug targeting and delivery
- The particles have diameters in the range of 1-100nm and are manufactured from inert materials such as gold, tin oxide and larger polymeric materials such as albumin
- In addition, there are numerous engineered constructs, assemblies, architectures, and particulate systems. These include polymeric micelles, dendrimers, polymeric and ceramic nanoparticles, protein cage architectures, viral-derived capsid nanoparticles, polyplexes, and liposomes
- Nanoparticles are already in use today as contrast agents for molecular imaging, being targeted to various disease-specific (bio)molecules, and in drugs, improving the drugs' effectiveness due to their large surface-to-volume ratio
- Nanoparticles are hoped to offer particular improvements in drug delivery specificity where targeted nanoparticles could hone in on only target cells without causing an immune response due to their biocompatible housing

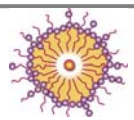
→ *Further analysis of nanoparticles and related areas can be found within the Nanomedicine Foresighting report, available on the ITI Life Science website*



The aim of nanoparticles is to deliver biological compounds to targeted sites of interest while minimising non-specific interactions

Benefits of Nanoparticles

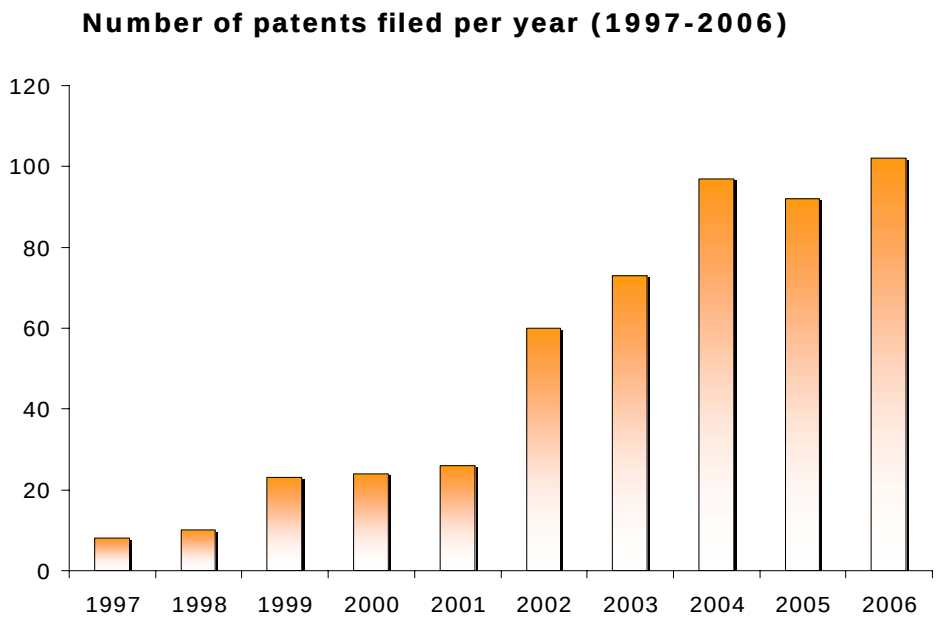
- Nanoparticles provide massive advantages regarding drug targeting, delivery and release and, with their additional potential to combine diagnosis and therapy, nanoparticles will emerge as one of the major tools in nanomedicine
- They can potentially even check for overdosage before becoming active, thus preventing accidental or intentional poisoning
- Despite the vast increase in complexity over present-day drugs, such agents, reproducibly produced via new technological principles based on self-assembly, could be totally ‘pure’ and predictable in their behavior
- The hope is that safety and efficacy may be inherent in the designs of such delivery vehicles, in which case regulatory issues could be simplified rather than complicated
- Nanoparticulate drug delivery systems have great potential in a wide range of applications such as anti-tumor therapy, gene therapy, AIDS therapy and radiotherapy
  - And also for the delivery of proteins, antibiotics, virostatics, vaccines and as vesicles to pass the blood-brain barrier



The goal is to develop inert carrier systems that will dramatically reduce patient side-effects and manufacturing batch variability

IP Landscape

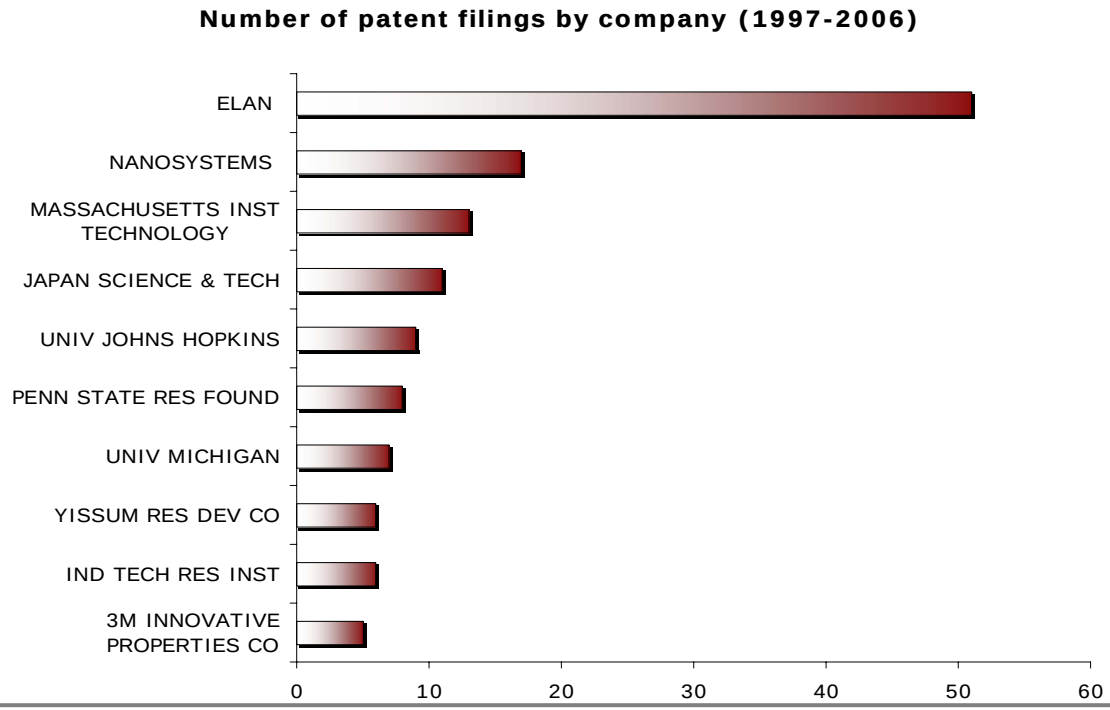
- There has been a substantial increase in the patent activity in the area of nanoparticles and encapsulation since 2001. Over 90 patent filings a year have been made since 2004
- Key words used for patent search were: nano, encapsulate, liposome or colloid (and drug delivery)



The nanoparticle area has seen an explosion of interest since 2001

Research Activity in Nanoparticles

- With over 50 patent filings since 1997, Elan easily dominate this field of research and patent filing. Central to Elan's success has been their NanoCrystal technology which it has licensed to a number of big pharma companies
- The majority of the other leading entities are research institutes although 3M Innovations also appears in the top 10, as well as being seventh in the transdermal drug delivery area

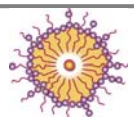


Elan is the key patent holder in this area with over 50 patents since 1997

Leading Companies

Company	Technology	Products	Comments
Acusphere	Hydophobic Drug Delivery System (HDDS)	Re-formulated paclataxel, AI-850 (PoC)	
Camurus	FluidCrystal nanoparticles: Cubosome, Hexosome, Flexosome	Phase II and earlier for cancer, drug addition and metabolic syndrome	
CytImmune Sciences	Pegylated Colloidal Gold Tumor-Targeting Nanotechnology	CYT-6091 (Ph I), CYT-21001 (pre-clinical)	Focussed solely on cancer
Do Coop Technologies	Neowater	Drug delivery service company for pharma and academia	
Elan	NanoCrystal	Technology licensed to Wyeth, Merck, Abbott and BMS	Market leading position
Imarx Therapeutics	MRX-801 microbubbles	SonoLysis (Ph I/II)	Uses ultrasound to break up clots
Lavipharm	Supercritical Fluids, Drug Crystal Dispersion, Drug Polymer Complexion	Range of generic brands but appear to be few using novel technologies	Leader in Greek market
Medipol SA	Hynosphere	Natural biopolymers: alginate, chitosan, modified cellulose and heparin	
Nanopharma Technologies	Nanoparticle Drug Delivery technology	Investigational	
NanoValent Pharmaceuticals	Polymerized Liposomal Nanoparticle (PLN)	Contract design and manufacture of PLN compounds for pharma and academia	
Shimoda Biotech	Capsivector Targeted Delivery Technology	Investigational	
ULURU	Hydrogel Nanoparticle Aggregate technology	Investigational	Also possesses a transmucosal drug delivery device (OraDisc)

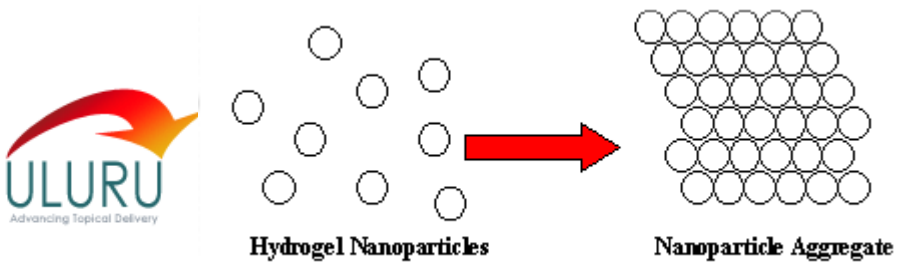
RED = case study



There is a number of products currently on the market as well as in clinical development that are using nanoparticles as a drug delivery mechanism

Case Study 1: Hydrogel Nanoparticles

- ULURU are developing a novel biomaterial that utilises hydrogel nanoparticle aggregates to form a material of varying strength and function. The aggregate is then implanted into the body to form a permanent, porous hydrogel implant
- The company has stated its intention to pursue the first application of this technology as a dermal filler, but a secondary application has been highlighted in drug delivery. This is done by incorporating the drug into the interstitial spaces between the nanoparticles during formation of the aggregate
- Interestingly, the size of these spaces can be tailored to the particular drug of choice and the company has been able to encapsulate proteins within the lattice, which are then slowly released from the aggregate once implanted in the body
- Moreover, as the drug / nanoparticle aggregation is performed in water solutions, this is an advantage over solvent solutions which are often used in other drug delivery materials

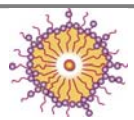


Nanoparticle technology can be combined with structural biomaterials to produce new ways of delivering drugs at the site of interest

Case Study 2: PEG-coated Nanoparticles

JOHNS HOPKINS UNIVERSITY

- In January 2007, researches at the Johns Hopkins University published a paper in the *Proceedings of the National Academy of Sciences* (PNAS) describing a way to transfer large nanoparticles quickly across mucous membranes by coating them in polyethylene glycol (PEG)
- Mucous membranes protect tissue from unwanted pathogens, however, in some diseases, these membranes become overly viscous and result in adverse symptoms, for example cystic fibrosis. The extra mucous also means it is even more difficult to treat such conditions with small molecules which struggle to cross the membranes
- The group was led by Associate Prof Justin Hanes and Dr Samuel Lai. They used PEG as it dissolves in water and has a net neutral charge – similar characteristics to the viruses they were studying that could move well through mucous barriers
- They discovered that nanoparticles coated in PEG moved through the mucous 1000 times faster than uncoated particles. Moreover, they also discovered that nanoparticles as large as 200-500nm were able to move quickly through the mucous mesh, and that these larger particles moved more quickly than smaller particles only 100nm wide. Previous work had suggested that in order to cross the mucous barrier the nanoparticles would need to be smaller than 55nm wide. Larger particles are better for prolonging drug release, and allowing for a wider range of encapsulates
- “These findings set the stage for a new generation of nanomedicines that can be delivered directly to the affected areas” Hanes said, and pointed towards delivering antibiotics, chemotherapy, nucleic acids and other compounds directly to the lungs, GI tract and cervicovaginal tract



Coating nanoparticles in PEG significantly improved their ability to cross mucous membranes

Case Study 3: Needle-free Vaccines

Grand Challenges in Global Health

- The use of needles to deliver vaccines is associated with a risk of infection (including HIV and hepatitis B & C) and problems regarding waste disposal. Nanoparticles are being investigated in the quest to overcome these issues and enable simple and safe needle-free vaccine delivery
- A number of influenza vaccines has been developed and launched, to varying success, but there remains a significant unmet need to develop ways of delivering other vaccines to the body in a cost-effective and efficacious way
- The Grand Challenges in Global Health initiative is a collection of NGOs that have made needle-free vaccines one of their grand challenges. In June 2005 the GCGH granted two nanoparticle grants :

A $6.3m grant went to James Baker at the University of Michigan's Nanotechnology Institute for Medicine and Biological Sciences (MNIBS) to develop its technology, NanoStat – a nanoparticle emulsion for delivering vaccines through the nasal mucous membranes

A $7.6m grant went to David Edwards, Harvard University's Gordon McKay Professor of Biomedical Engineering in the Division of Engineering and Applied Sciences for the development of nanoparticle aerosols that could deliver vaccines by inhalation, particularly TB

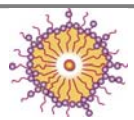
MNIMBS

Harvard University School of Engineering and Applied Sciences

Nanoparticles are being developed to deliver vaccines through the lungs and nose without the need for syringes – thus reducing the risk of infection and needle-stick injury

Nanoparticle Innovation Barriers

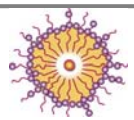
- Solubility
  - Therapeutic and diagnostic agents can be encapsulated, covalently attached, or adsorbed on to nanocarriers. These approaches can easily overcome drug solubility issues, particularly with the view that large proportions of new drug candidates emerging from high-throughput drug screening initiatives are water insoluble
  - But some carriers have a poor capacity to incorporate active compounds (e.g., dendrimers, whose size is in the order of 5–10 nm). There are also alternative nanoscale approaches for solubilisation of water insoluble drugs
  - One approach is to mill the substance and then stabilise smaller particles with a coating; this forms nanocrystals in size ranges suitable for oral delivery, as well as for intravenous injection. Thus, the reduced particle size entails high surface area and hence a strategy for faster drug release
- Stability
  - The main pharmaceutical goals for future developments in drug delivery systems are: to improve their stability in the biological environment; the bio-distribution of active compounds; the drug loading; targeting; transport; release and interaction with the biological barriers
  - The cytotoxicity of nanoparticles or their degradation products remain one of the major problems and improvements in biocompatibility obviously are a main concern of future research



Product solubility and stability are two major areas where challenges remain and will require further technological innovation

Application of Nanoparticles

- Specific therapeutic applications of nanoparticles include the development of:
  - Targeted devices capable of bypassing biological barriers to deliver multiple therapeutic agents at high local concentrations, with physiologically appropriate timing, directly to **cancer** cells
  - Non-invasive diagnosis and targeted therapy of vulnerable **atherosclerotic plaque** with new approaches in imaging and plaque stabilization by removal of e.g. oxidised lipoprotein, and nanodevices attaching to unstable plaque, potentially 'broadcasting' external warnings of plaque rupture
  - Devices to monitor **thrombotic** and **hemorrhagic** events can have a high impact, e.g., in the diagnosis and treatment of stroke and embolisms. Multifunctional devices could detect events and transmit real-time biological data externally
  - Tissue repair and **regeneration** in the area of tissue scaffoldings for the bioengineering of heart or lung tissue or the production of vascular grafts, supported by biodegradable nanoparticles which release appropriate growth factors and angiogenic factors to build functional tissue
  - Applications which improve the understanding of brain function and diagnose and treat neurodegenerative diseases like **multiple sclerosis**, **Alzheimer's disease**, **Parkinson's disease** and potentially widespread diseases like migraine and depression

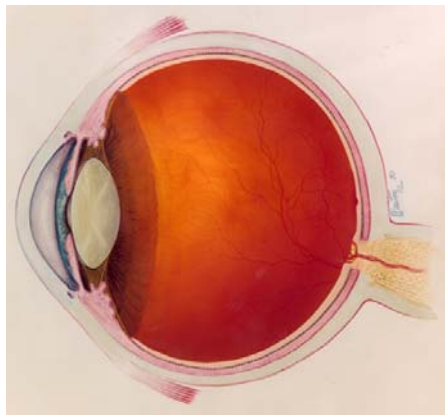


Nanoparticles lend themselves to a broad range of therapeutic and diagnostic delivery mechanisms, including oral, inhaled, injectable and transdermal routes

Foresighting Areas

- Transdermal
- Microcapsules
- Nanoparticles
- **Ocular Delivery**

- Background
- IP Landscape
- Research Activity
- Anterior Delivery
- Posterior Delivery
- Leading Companies
- Case Studies x 3



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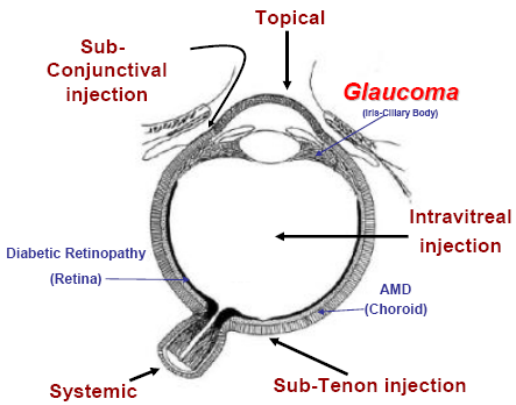
Ocular Delivery Background

- The eye is a uniquely isolated organ and has remained largely untouched in terms of effective drug delivery mechanisms. For example, the traditional means of delivering drugs to the anterior part of the eye, to treat conditions such as glaucoma and conjunctivitis, is topical administration of eye drops. However, it is estimated that only 5% of the applied solution is absorbed into the anterior eye, the rest being washed away in the tears
- In recent years methods have been developed to access the posterior section of the eye to treat conditions such as age-related macular degeneration and diabetic retinopathy. As so little of the drug is absorbed into this part of the eye, this has involved an injection directly into the vitreous
- As this intravitreal injection is a very invasive procedure that needs to be repeated, this method has significant issues around patient tolerability. Hence there remains a significant need for new ways to introduce biological compounds non-invasively into both the anterior and posterior parts of the eye

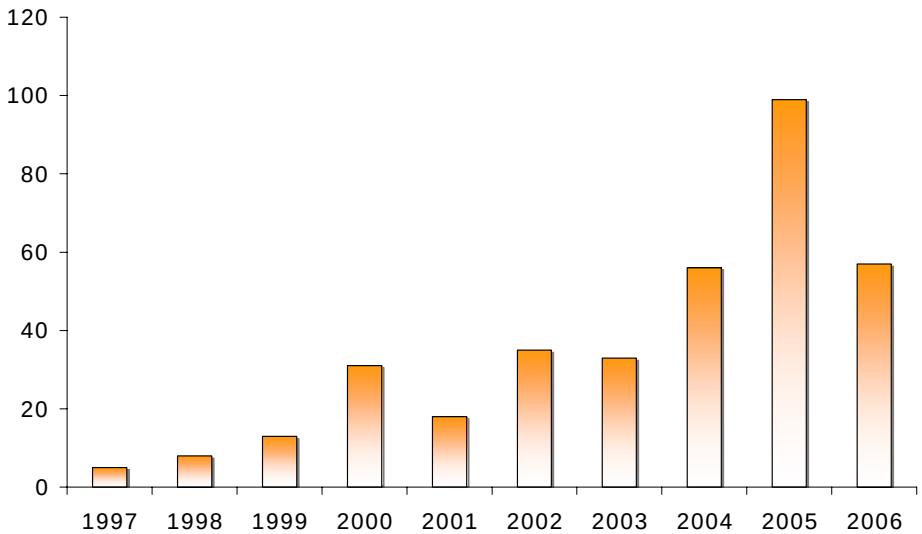


The eye presents particular challenges for drug delivery and both invasive and non-invasive methods have been developed

IP Landscape

- The eye has been an active area for patents, peaking in 2005 with almost 100 patents filed in this year. Of note in the past year we would highlight the July 2007 filing of Acoint's method for minimally-invasive delivery of therapeutic products into the eye by applying electrical current to a drug reservior
- Key words used for patent search were: ophthalm(*), ocular, optic, eye, retina, cornea, transocular, intravitreal, polymeric adj hydrogel, or transscleral (and drug delivery)

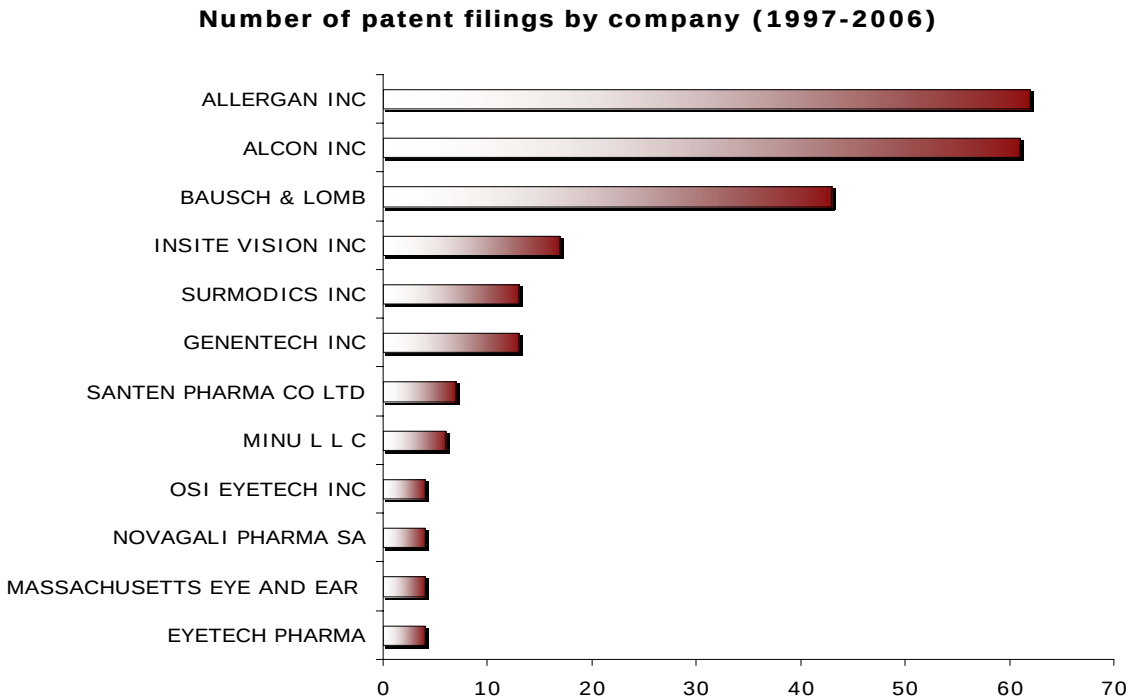
Number of patents filed per year (1997-2006)



The delivery of drugs to the eye has been an increasingly active area for patent filings

Research Activity in Ocular Delivery

- The research activity within the ocular drug delivery area clearly shows the dominance of the leading eye-care specialists with virtually all of the top 10 entities being companies specialising in this field
- Together, Allergan, Alcon and Bauch & Lomb account for 72% of all patents filed by the top 10



Research activity in the ocular drug delivery area is dominated by the leading specialist companies in this field

Anterior Eye Delivery

- **Ophthalmic nanoparticles** are being developed to be administered topically in order to offset some of the disadvantages of this route of administration. However, this technology also faces its own challenges, including: formulation stability; particle size uniformity; control of drug release rate; and large-scale manufacture of sterile preparations
- **Contact lenses** coated in polymeric hydrogels, there are six methods described:
  - 1. Pre-soaking of contact lenses with the drug – depends on water content, thickness of lens, molecular weight of drug, concentration of drug loading solution, solubility of drug in gel matrix and the time the lens remains in solution. But could only deliver drugs for a few hours
  - 2. Hollow cavity - oxygen and carbon dioxide permeability was lower than recommended
  - 3. Drug-containing liposomes bound to surface of lens
  - 4. Dispersing mico-emulsion drug drops
  - 5. Binding ionised drugs to ion ligands in the lens, releasing through ion exchange
  - 6. Molecularly imprinting the lens
- **Iontophoretic** drug delivery – used by EyeGate Pharma to deliver corticosteriods

In order to improve on standard topical eye drops there is a number of areas being investigated in anterior drug delivery

Posterior Eye Delivery

- **Intravitreal injections** have become increasingly accepted in recent years following the launch of Macugen and Lucentis for the treatment of age-related macular degeneration (AMD)
  - Although effective, the injections need to be repeated and can lead to injection site irritation and changes in ocular pressure
- **Intravitreal inserts** of sustained-delivery devices have been widely used in recent years and are effective in treating a number of important conditions, but they also have a number of drawbacks, including:
  - Difficult to insert; easy to misapply; expensive to manufacture; can lead to localised irritation; inflammation and infection; operations often require specialist practitioners
- Recent work has focussed on reducing the number of interventions required by delivering **encapsulated cells** to the posterior section of the eye, which can then deliver the desired compound over a longer period of time
  - An example of this is Neurotech's encapsulated cell technology which has demonstrated delivery of protein over 18 months. The company's lead compound NT-501 is in Phase II/III trials in the US for retinis pigmentosa

Injecting or implanting in the posterior eye is an effective way to deliver biologicals, but is very invasive and can lead to complications

Leading Companies

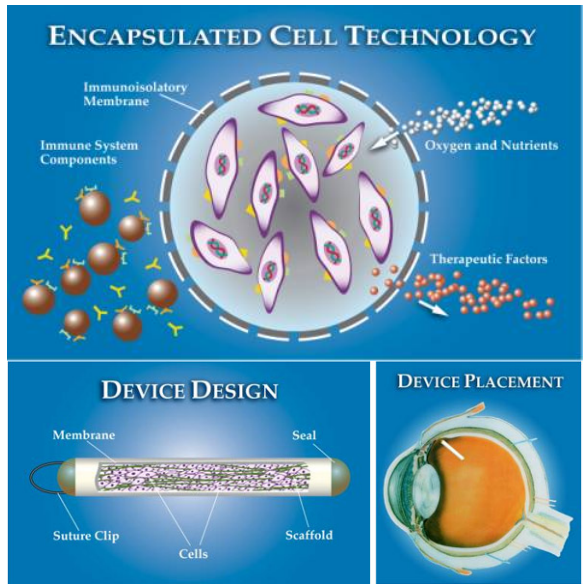
Company	Technology	Products	Comments
Alcon	Contact lenses, eye drops	Numerous topical Rx treatments for ocular diseases	Market leader in topical formulations. First injectable product Triesence approved in November 2007
Allergan	Eye drops	Numerous topical Rx treatments + intramuscular injection (Botox)	
Bausch & Lomb	Contact lenses, eye drops intravitreal implants	Retisert, Vitrasert + Rx topical treatments	Licensed from pSivida and Chiron Vision, respectively
Biopolymer Innovations LLC	OcularGel Drug Delivery System	Investigational	
CIBA Vision	Contact lenses	Lots of lens care products	
EyeGate	Coulomb Controlled Iontophoresis (CCI)	EyeGate II delivery system	Uses iontophoresis to deliver therapeutics
Genentech	Intravitreal injection	Lucentis (fragment of Avastin)	
InSite Vision	DureSite polymeric matrix	AzaSite (in collaboration with Inspire Pharma)	
Neurotech	Encapsulated Cell Technology	NT-501 for retinis pigmentosa (Phase II/III)	
Neuroptix	Quasi-Elastic Light Scattering + Fluorescent Ligand Scanning		Optical diagnostic of Alzheimer's disease
Novagali Pharma	Novasorb, Eyeject	Cationorm , Nova22007, Vekacia, Nova21048, Nova21046, Nova21027, Nova22038, Nova63035	
OSI		Macugen	
pSivida	Intravitreal implants	Retisert, Medidur (in collaboration with Alimera Sciences)	Also uses BioSilicon technology for oncology indications. Licensed to Pfizer in April 2007
Regeneron		VEGF Trap-Eye	
Surmodics	I-vation Sustained Drug Delivery Implant + RetinaJect	I-vation TA (triamcinolone acetonide)	Collaboration with Merck in June 2007 for I-vation TA, expanded in January 2008 to include an unknown drug
QLT Inc	Ocular punctal plug drug delivery system	Visudyne (iv injection)	

R&D in the ocular drug development market is driven by small biotech companies with innovative technology

RED = case studies

Case Study 1: Neurotech's NT-501

- Since the launch of pSividia's Retisert, surgical implants have been gaining acceptance as a delivery mechanism to the posterior part of the eye
- The last innovation comes from Neurotech's Encapsulated Cell Technology (ECT), which describes the implanting of genetically-modified human cells packaged in a semi-permeable hollow fibre 6mm long membrane
- In order to enable long-term cell survival the membrane allows the influx of oxygen and nutrients while simultaneously preventing direct contact with the body's immune system
- In return, the cells continuously produce the therapeutic protein which diffuses out of the implant. Proof of concept studies have demonstrated the ability of this technology to deliver CNTF into the vitreous cavity of rabbit eyes consistently for 18 months
- Interestingly, Neurotech are able to engineer the cells to produce various factors to treat conditions such as degeneration of photoreceptors and/or ganglion cells in the neural retina, vascular proliferation and inflammation
- The lead product, NT-501 is currently in Phase II/III trials for the treatment of retinis pigmentosa



Neurotech are pioneering the implantation of encapsulated cells into the posterior section of the eye to deliver therapeutic proteins

Case Study 2: EyeGate's EyeGate II

- As highlighted previously the eye presents particular challenges in seeking to deliver compounds to the area of interest, whether that be the anterior or posterior sections. In response to the need for a non-invasive method to deliver therapeutics effectively to the eye EyeGate Pharma developed the EyeGate II delivery system
- The EyeGate II uses coulomb controlled iontophoresis (CCI) that delivers products to the eye through an iontophoretic reservoir that sits on top of the cornea. The method uses similar principles to the active patch system developed by Vyteris to deliver products transdermally
- The current focus is on delivering pain medications, anti-inflammatories and corticosteroids to the eye. A clinical study in acute uveitis is planned for Q1/Q2 2008
- Before it can be used, the compound needs to be formulated for iontophoretic delivery. Key criteria in determining potential for re-formulation are: overall compound charge; solubility in aqueous solutions; and stability
- The company also state that this technology could be used for both anterior and posterior drug delivery, with contact with the eye being between 3-5 minutes for most drugs
- The company is currently investigating the possibility of delivering larger biologics, including peptides, proteins and oligonucleotides

EyeGate are developing a non-invasive trans-scleral delivery device that can deliver compounds to both the anterior and posterior eye

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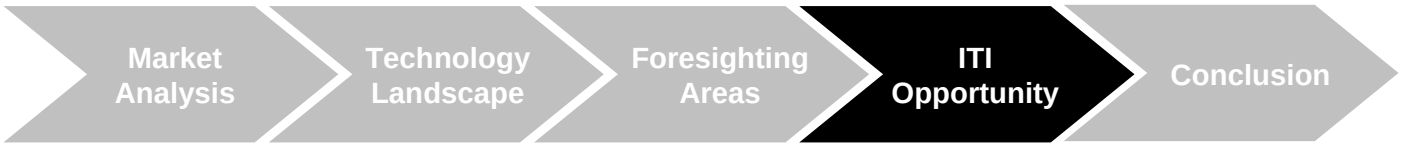

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Future Trends in Drug Delivery

Pharma & Biotech Industry

- Drug delivery will remain an area of keen interest for companies within the global healthcare market
- We expect the majority of new technologies to come out of academic- and industry-sourced start-up companies and specialist biotechs. Validating their technology through proof-of-concept trials with a key compound will be vital to securing both financial investment and the interest of larger companies
- Hence, we believe big pharma will continue to seek to acquire or license such proven early-stage technology companies, in an attempt to accumulate a portfolio of in-house technologies that can be used to develop their own candidates

Patients/Consumers

- Due to the technological advances that have been readily adopted by modern society (mobile communications, cutting-edge imaging techniques, genetic profiling) there is an attitude of general acceptance to the latest innovations, for example drug deliveries associated with regenerative medicines
- As the demographics of many Western countries shift towards a more elderly population, we expect a greater appetite for preventative technologies and drug delivery innovation

Sizeable opportunities exist for companies with a proven drug delivery technology

Future Trends, continued

Healthcare organisations

- With ever increasing pressure on costs from healthcare organisations, only delivery technologies that have demonstrated significant improvements to patient care can secure the premium prices necessary to recoup years of R&D investment
- A small increase in patient convenience is unlikely to convince payers of the cost-effectiveness of the delivery technology – as observed recently with the failure of the first inhaled insulin, Exubera

Therapeutic Focus

- Despite the problems with inhaled insulin, we expect the delivery of biologics to the body to remain an area of intense R&D, due to the high commercial rewards for improving the delivery of this group of compounds to the body
- The failure of inhalation to provide the answer to delivering macromolecules, means there remain great rewards for the safe delivery of macromolecules orally. Technologies such as nanoparticles and microcapsules could begin to unlock the key to this delivery in the future
- Moreover, increasing the specificity of targeted compounds, particular cancer drugs, will remain a key focus for technology innovations

But only technologies generating truly significant improvements in patient care will be rewarded in the marketplace

Foresighting Area Trends

Transdermal

- Advances in active patch technology have increased the range of potential compounds that could be delivered across the skin to those with a molecular weight of around 6,000–8,000 Da. We expect additional technologies to emerge that will push the upper limit of this range and enable even larger compounds to be delivered

Microcapsule

- It is only recently that the microcapsules have been viewed as potential drug delivery devices. While research is still in the early stages we expect initial work will focus on the use of oral microcapsules to deliver compounds that cannot be formulated into traditional capsules

Nanoparticle

- Nanoparticles have enormous application in drug delivery. Recent work on improving the delivery of nanoparticles through mucous membranes could lead to dramatic improvements in disease states such as cystic fibrosis. Moreover, as nanoparticles become better understood we expect advances in diseases where target selectivity is a high priority, such as cancer

Ocular delivery

- The eye provides an extremely robust natural barrier. The key challenge is to deliver compounds non-invasively to the inside of the eye. We expect new technologies to emerge which seek to answer this problem and generate significant improvements in patient care

Scottish Drug Delivery Fit

Transdermal

- Strathclyde Innovations in Drug Research
- ProStrakan, Galashiels
- Controlled Therapeutics (Hydrogel), East Kilbride

Nanotechnology

- The Institute of Nanotechnology, Stirling
- Nanomerics, Glasgow
- XstalBio, Glasgow
- Kelvin Nanotechology, Glasgow
- Prof Cronin, University of Glasgow
- Strathclyde Innovations in Drug Research
- Dr Cheng, Robert Gordon University, Aberdeen

Microcapsules

- Strathclyde Innovations in Drug Research
- XstalBio, Glasgow

Ocular drug delivery

- Scottish Ophthalmology and Imaging Consortium
- Optos, Dunfermline
- Institute of Nanotechnology, Stirling
- Prof Wilson, Strathclyde University
- Institute of Photonics, Strathclyde University

Drug delivery related research in Scotland is particularly strong in transdermal, nanotechnology and ophthalmology

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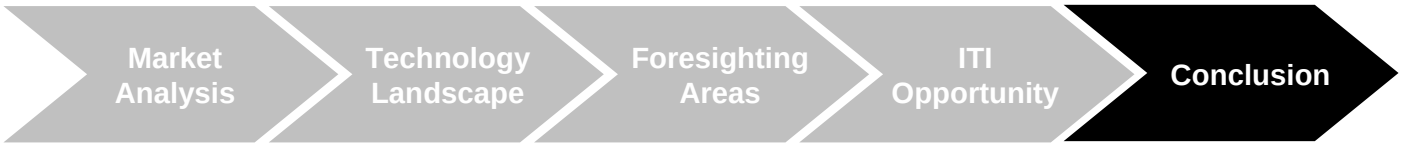

Conclusion

- The drug delivery sector is an **extremely broad and complex area** combining elements of the medical device and pharmaceutical industries. This makes for an interesting and rapidly changing area within the healthcare market
- A vital element in **driving value** in this market is to get the greatest possible use out of a technology, either by using it to deliver as wide a range of compounds as possible to the same part of the body, or by finding new ways to deliver compounds to different parts of the body
  - A good example of this is the way that iontophoresis has formed the backbone of both Vyteris' transdermal patch and EyeGate's ocular delivery device. This makes this market a very difficult one to compartmentalise and categorise
- Conversely, this fluidity also means drug delivery is an area of **high innovation**, where advances in one area can quickly lead to advances in another unrelated area.
  - A good example of this is the field of nanoparticles, where advances in the understanding of how to deliver these particles through membranes could have utility in a wide range of delivery mechanisms from nasal sprays to ocular emulsions
- We expect this '**cross-fertilisation**' to continue and lead to the emergence of new delivery platforms that will answer some of the current drug delivery innovation barriers of accessibility, selectivity, stability and safety

ITI see potential for value creation in Scotland in the area of drug delivery

Next Steps

- ITI are actively seeking opportunities in these areas and welcome collaborations with members and specialists in these areas
- Given Scotland's expertise in nanotechnology and ophthalmology, these two areas provide attractive leads for further investigation of cutting-edge drug delivery technology
- If you would like to discuss the report findings and associated opportunities with us further, please contact ITI Life Sciences at:
  - foresighting@itilifesciences.com
  - Tel. +44 (0)1382 568060
- For more information on ITI Life Sciences, please visit
  - http://www.itilifesciences.com/

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