RECENT ADVANCES IN IMPLANTABLE DRUG DELIVERY

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ABSTRACT

Recently Implantable drug delivery is one of the technology sector that often overlooked in the development of new drug delivery by the formulation, research and development in many pharmaceuticals. Implant drug delivery technologies have ability to reduce the frequency of patient driven dosing and to deliver the compound in targeted manner. Many product utilizing implant delivery technologies are being utilized for many therapeutics applications such as, dental, ophthalmic, oncological disease. Based on this groundwork the aim of present review is to focus on recent technologies in implantable drug delivery.

Keyword: Recent technologies, Implantable drug delivery, Therapeutics application in oncology and ophthalmic disease.

INTRODUCTION

Orally administered drug must be protected against denaturation in the gastrointestinal tract and should be capable of absorption across the wall of the stomach or the intestine. After absorption and upon reaching the portal circulation, it must be resistant to hepatic enzymes. The rate of drug absorption and elimination should ensure the blood levels within the therapeutic range. Moreover, the amount of intact drug that reaches the site of action should be sufficiently large to obtain desired therapeutic effect but insufficient to cause untoward side effects.[1]

A controlled drug action may be achieved by either chemically modifying the drug moiety or by formulating it in a specific way to control its release. Oral controlled release dosage forms can provide efficacy for about 24hrs. The main drawback of oral dosage form is the long transit time of approximately 12hrs through the GIT. If drug cannot be administered orally, a parenteral route of delivery is an alternative.

Many proteins/peptides and other drugs, which are susceptible to the adverse conditions of GIT, are administered intravenously. Unfortunately, in intravenous drug administration, the duration of drug action is short for majority of therapeutically active agents and therefore frequent injections are required. The development of injectable controlled-release dosage forms is more likely to succeed commercially than alternative routes of delivery, assuming that these dosage forms provide the desired efficacy and safety.

In case of topical drug administration, the percutaneous absorption of most drugs is limited due to physiological characteristics of the drugs and presence of highly impermeable stratum corneum.

Implantable drug delivery devices are devoid of aforementioned limitations associated with oral, intravenous, topical drug administration vis-à-vis subcutaneously implantable drug delivery devices offer one unique advantage of a retrievable mechanism. [1]

For incorporation of a variety of therapeutic agents with different physicochemical properties and for better control of drug release, number of excipients is now used. Thus, more recent implants usually contain the drug in a rate controlling systems. These systems are available in a variety of sizes and shapes.

Desirable Properties of Effective Subcutaneous Controlled Drug Delivery System

- It should improve patient compliance by reducing the frequency of drug administration over the entire period of treatment.
- It should be free from any major surgical procedure and ideally should be readily administered.
- It should release the drug in a rate-controlled manner, which leads to enhanced effectiveness and reduction in side effects.
- It should be readily retrievable by medical personnel to terminate medication.
- It should be easy to sterilize.
- It should be easy to manufacture and relatively inexpensive.
- It should be devoid of any potential medical complication.
- It should be stable and safe, and should have good mechanical strength.

Some of the approved implant products include Leuprolide acetate and Nafarelin acetate in biodegradable PLGA copolymer for one-month release (Lupron® depot microspheres, TAP and Zoladex® pellet, ICI, respectively). Also new on the market is a silicone polymer capsule system containing Levonorgestrone for five-year contraception (Norplant, Wyeth-Ayerst)[1-4]. In

addition, several implantable pumps for prolonged drug delivery are available commercially.

RECENT TECHNOLOGY IN IMPLANTABLE DRUG DELIVERY:

DURIN™ TECHNOLOGY

The DURIN™ biodegradable implant technology is a platform for parenteral delivery of drugs for periods of weeks to six months or more. The technology is based on the use of biodegradable polyester excipients, which have a proven record of safety and effectiveness in approved drug delivery and medical device products. [3]

Features:

- Superior delivery kinetics.
- Flexibility.
- Superior drug loading and stability.
- Fully biodegradable.
- History of safe human use.
- Cost effective.

The **DURIN™ biodegradable implant technology** is based on the use of biodegradable polyesters as excipients for implantable drug formulations, includes the polymers and copolymers prepared from glycolide, DL-lactide, L-lactide, and €-caprolactone.

The degradation times and physical properties of the biodegradable excipient can be engineered to achieve a wide variety of drug delivery goals by adjusting monomer composition and distribution, polymer molecular weight, and end group chemistry.

The overall form of the implant is typically a small rod or pellet that can be placed by means of a needle or trochar. The composition of the rod or pellet can be monolithic, where the drug is uniformly dispersed throughout the excipient. Alternatively, reservoir-type designs are also possible in which the rod or pellet is composed of a drug-rich core surrounded by a rate-controlling membrane.

The drug and excipient are mixed together, and the mixture is formed into a fiber, rod, tablet, or pellet by an extrusion or molding process. The rate controlling membrane, if required, may be applied during or subsequent to the core-forming process.[5]

Manufacturing:

Typically, melt extrusion is used at modest temperatures to produce biodegradable implants for drug delivery. The active and excipient are combined and fed to a melt extruder to produce a bulk rod, which is then cut to produce the unit dose. For coaxial, membrane-controlled implants, two extruders are operated to simultaneously produce the core and membrane in a continuous process. For particularly heat labile compounds, the DURIN™ technology is also compatible with proprietary manufacturing methods other than extrusion that ensure drug stability. Because DURIN™ implants are produced using continuous manufacturing processes, batch size is determined by the length of the extrusion run. Several clinical batches of biodegradable implants at a batch size of more than 2000 doses are successfully prepared. [4]

ATRIGEL® DRUG DELIVERY TECHNOLOGY

The Atrigel® system is a proprietary delivery system that can be used for both parenteral and site-specific drug delivery. It consists of biodegradable polymers dissolved in a biocompatible carrier. When the liquid polymer system is placed in the body using standard needles and syringes, it solidifies upon contact with aqueous body fluids to form a solid implant [6]

Atrix Laboratories has continued to develop the technology and to extend its use to a large number of both drug delivery and medical device applications.

The manufacturing process for the Atrigel® system is not complicated in that the first step is the dissolution of the polymer into a biocompatible solvent. The drug is next added to the solution where it dissolves or forms a suspension. This drug/ polymer mixture is then easily and conveniently injected into the body where it forms a solid implant inside the tissue. The ease of manufacture of the Atrigel® system and its relatively pain-free subcutaneous injection into the body provide significant advantages over both solid implants and microparticles.[7.]

These include the polyhydroxyacids, polyanhydrides, polyorthoesters, polyesteramides, and others. The polymers most often used are poly (dllactide), lactide/glycolide copolymers, and lactide/caprolactone copolymers because of their degradation characteristics and their approval by the Food and Drug Administration (FDA).[8]

The solvents employed in the Atrigel system to dissolve the polymers range from the more hydrophilic solvents such as dimethyl sulfoxide, *N*-methyl-2-pyrrolidone (NMP), tetraglycol, and glycol furol to the more hydrophobic solvents such as propylene carbonate, triacetin, ethyl acetate, and benzyl benzoate. The most frequently used solvent is NMP because of its solvating ability and its safety/toxicology profile.[9, 10]

Manufacturing, sterilization, and packaging

Because the Atrigel® system is a somewhat viscous polymer solution, it is not as easy to fill into vials and aspirate into syringes at the time of use as normal aqueous solutions. Therefore, the products currently marketed using this technology are filled into plastic syringes and packaged with foil-lined material to protect from moisture. Atrix Laboratories has developed custom-made equipment to fill a variety of plastic syringes with the polymer solutions within narrow fill volumes.

Although an Atrigel® polymer solution can be sterile-filtered, this is not the preferred method because of the viscosity of the solution. Therefore, gamma irradiation was evaluated and found to be a convenient method of terminal sterilization of the polymer solution. There is some loss in polymer molecular weight during gamma

irradiation, but this is compensated for by using a polymer with a slightly higher molecular weight initially [6].

Scale-up process

The manufacturing of products with the Atrigel® system can easily be scaled up to commercial quantities. First, the polymer is dissolved into the biocompatible solvent using a standard pharmaceutical product mixer. More recently, the polymer has been dissolved in the solvent by simply loading the two components into a sterile plastic container and placing it on a roll mixer. The polymer solution is then transferred from the plastic container to the syringe-filling equipment where it is loaded into individual syringes. The plastic container can then be discarded and the need for thorough cleaning is eliminated. The filled syringes are capped and placed into foil-lined packages to prevent moisture absorption. The drug is either powder-filled or lyophilized into syringes. If the drug is stable to gamma irradiation, then both the drug and polymer syringe are terminally sterilized by this method. If the drug is not stable to gamma irradiation, then the lyophilization is carried out under aseptic conditions to give a sterile drug syringe, and the polymer solution is sterilized by gamma irradiation. With this type of process, the manufacturing can easily accommodate the production of several hundred syringes to thousands in one batch[11].

In some cases, both the drug and polymer are stable as with the lidocaine hydrochloride product. However, because the drug and polymer are in solution, degradation of both components and reactions between the two may occur somewhat faster with some formulations than in a dry, solid state. With such type of products, the drug and polymer solution are maintained in separate syringes until immediately before use. Atrix has developed proprietary methods to lyophilize drugs in plastic syringes that can be coupled with the polymer solution.

Four products have already been approved by the FDA using the Atrigel technology.

1) Atridox® periodontal treatment product

2) Atrisorb® GTR barrier product

3) Atrisorb® D product with Doxycycline

4) Doxyrobe® product

1). ATRIDOX® periodontal treatment product

Dosage and administration

Steps:

Figure 1. (a)

Couple Syringe 1 (liquid delivery system) and Syringe 2 (drug powder).

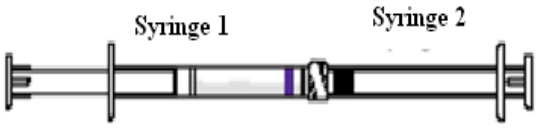

Figure 1. (b)

Inject the liquid contents of Syringe 1 (indicated by purple stripe) into Syringe 2 (Doxycycline powder) and then push the contents back into Syringe 1. This entire operation is one mixing cycle.

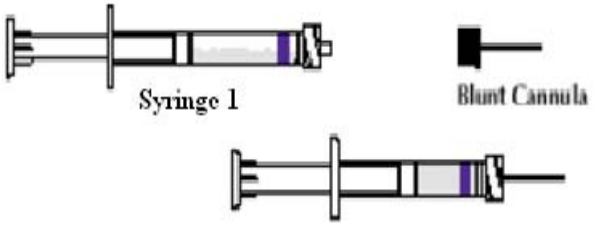

Figure 1. (c)

The contents will be in Syringe 1 (indicated by purple stripe). Now hold the coupled syringes vertically with Syringe 2 at the bottom. Pull back on the Syringe 1 plunger and allow the contents to flow down the barrel for several seconds. Uncouple the two syringes and attach one of the provided cannulae to Syringe 1 Ready for injection.[11]

2). ATRISORB® Free Flow Bioabsorbable (GTR) Barrier

ATRISORB Free Flow Bioabsorbable (GTR) Barrier is a flowable gel that forms over a bone graft creating a barrier at the Guided Tissue Regeneration (GTR) surgical site which allows cell regeneration. It eliminates cutting, trimming, or handling of preformed barriers and reduces surgical time. ATRISORB is a unique flowable polymer that readily adapts to root morphology.[11]

3). ATRISORB®-D Free Flow Bioabsorbable (GTR) Barrier

ATRISORB-D contains all the advantages of ATRISORB, plus it is the only barrier that contains an antibiotic - doxycycline (4%). This provides a controlled release of doxycycline for a period of 7 days and is proven to prevent bacterial colonization of the barrier.[11]

4). ATRIDOX® (doxycycline hyclate) 10%

ATRIDOX is a Locally Applied Antibiotic (LAA) for the management of periodontal disease. When mixed, ATRIDOX becomes an easy to inject gel that flows easily to the bottom of pockets and fills even the smallest spaces between teeth and gums. It is these pockets and spaces where bacteria thrive and where ATRIDOX begins to work. It provides a controlled release of doxycycline for a period of 21 days6 and is bioabsorbable - no removal required. Atridox takes only minutes to prepare and administer at the chairside. ATRIDOX is patient friendly, no anesthesia is required.[11]

REGEL® DEPOT TECHNOLOGY

ReGel® is one of MacroMed's proprietary drug delivery systems. The leading product of MacroMed, ReGel®, employs 23% (w/w) copolymer of poly (lactide-co-glycolide)-poly (ethylene glycol) – poly (lactide-co-glycolide) (PLGA-PEG-PLGA) in phosphate buffer saline.

Research on poly (lactide-co-glycolide) and poly (ethylene glycol) polymers has resulted in an extensive database for clinical safety and efficacy as components in drug delivery systems.

Thermally reversible gelling materials, such as ReGel®, are a unique class of compounds being developed for parenteral delivery. ReGel® is a family of polymers that offer a range of gelation temperatures, degradation rates, and release characteristics. The thermal characteristics of ReGel®, which are in general terms a function of the molecular weight, degree of hydrophobicity, and polymer concentration, allow the necessary flexibility to match a variety of compounds to a convenient formulation for programmed delivery of active agent.

Examples of thermosensitive polymers

Poly (*N*isopropylacrylamide) (PNIPAAM), poly (ethylene oxide)- poly (propylene oxide)-poly (ethylene oxide) triblock copolymers (PEO-PPO-PEO), poly (ethylene glycol)-poly (lactic acid)-poly (ethylene glycol) triblocks (PEG-PLAPEG). Triblock PEO-PPO-PEO copolymers (Pluronics® or Poloxamers®) show gelation at body temperature at concentrations greater than 15% (w/w).

Procedure:

The synthetic process is well characterized and allows specified gelation temperatures to be produced based on the starting composition of the poly (ethylene glycol), lactide, and glycolide mixture. The components are poly (ethylene glycol), lactide, and glycolide monomers, and the catalyst is stannous octoate, which results in greater than 95% yield and more than 99% purity. Aqueous purification and sterilization via filtration or gas-sterilization of the lyophilized product is done.[12]

Administration:

Prior to injection, the product is reconstituted yielding aqueous ReGel® as a free-flowing liquid below its gelation temperature with a viscosity of < 1 poise. Following injection, the physical properties of the polymer rapidly undergo a reversible phase change that results in hydrophobic polymer-polymer interactions and the formation of a water insoluble biodegradable implants. The transition occurs without chemical modification of the triblock copolymer or active agent because ReGel is a physically formed thermally reversible hydrogel.[13]

Product Under clinical trials:

MacroMed's first product, **OncoGel®**, is supplied as a frozen formulation of paclitaxel in **ReGel®** and is entering Phase II trials.

Cytoryn™ is MacroMed's immunomodulatory localized peri-tumoral/intra-tumoral delivery system based on a combination of lymphokine interleukin 2 (IL-2) in ReGel®.[13]

ALZAMER® DEPOT™ TECHNOLOGY

The Alzamer® Depot™ technology was designed to offer sustained delivery of therapeutic agents, including proteins, peptides, other biomolecules, and small-molecular-weight compounds, for up to a month with minimal initial drug burst, and bioerosion of the dosage form.[14,15] The Alzamer® Depot™ technology consists of a biodegradable polymer, a solvent, and formulated drug particles. The depot is injected subcutaneously, and drug is released by diffusion from the system while water and other biological fluids diffuse in. At the later stages of release, the polymer degrades, further contributing to drug release. Microspheres, however, typically require complex production processes and harsh solvents that then require removal[16, 17.] Solution depot formulation processes tend to be simpler, typically involving only biocompatible solvents as part of the depot platform[18.]

Initial drug release from microspheres and these earlier-generation depot formulations tends to be rapid; up to 50% of the drug can be released upon injection. In contrast, Alzamer® Depot™ technology (ALZA Corporation, Mountain View, CA) uses biocompatible solvents of low water miscibility, which help control the initial drug release. In addition, this type of depot is easy to process and can be stored with the protein particles preformulated into the gel, enhancing convenience of use [19, 20, 21.]

Formulation development

Alzamer® Depot™ technology consists of the biodegradable polymer polylactic glycolic acid (PLGA), a biocompatible solvent of low water miscibility (e.g., benzyl benzoate), and formulated drug particles. Protein stability is maintained by isolating the drug in a solid particle. This particle is suspended in the non-aqueous polymer/solvent depot to prevent premature exposure to water. Drug release can be adjusted by varying the initial formulation and drug loading, as well as the injection volume of the preloaded syringe.

Pre-clinical evaluation

To date, more than 100 different Alzamer® Depot™ formulations have been tested in rats. No remarkable adverse clinical observations or systemic signs of toxicity have been noted.

SABER™ DEPOT TECHNOLOGY

The SABER™ Delivery System is an injectable, biodegradable delivery system technology that uses a high viscosity carrier such as sucrose acetate isobutyrate (SAIB), solvent and one or more pharmaceutically acceptable additives.[22]

In the simplest case, the high-viscosity SAIB is formulated as a low-viscosity liquid by mixing with a pharmaceutically acceptable solvent. The drug to be delivered is dissolved or dispersed in the SAIB/solvent solution for subsequent injection subcutaneously or intramuscularly. If a water-soluble solvent such as ethanol is chosen, the solvent will diffuse out of the injected volume leaving a viscous depot of SAIB and drug. The use of a more hydrophobic solvent such as benzyl benzoate gives a less viscous depot with slower solvent diffusion. Sustained drug release occurs over a period from several hours to several weeks by diffusion.

In some applications, an additive is used to affect release kinetics, drug stability, or other performance parameters. SAIB degradation follows drug release.

Manufacturing:

SAIB-based products are manufactured in a liquid mix-and-fill process using conventional tanks and stirrers. For dispersed drugs, particle size of the drug must be controlled, and particle size reduction is done by milling. Homogenizers have been used to disperse some of the drug suspensions.

Because the SABER™ technology is manufactured as a mix-and-fill liquid formulation, there have been no specific scale-up problems. Two issues that must be considered are transferring the high-viscosity raw material SAIB and the use of organic solvents. The use of solvents imposes certain limits on contact surfaces and requires particular attention in selecting tubing and seals. [23, 24].

Market products:

The most significant product on the market is **Lupron®** Depot, the leuprolide acetate microsphere product based on poly(dl-lactide) (PLA), and poly(dl-lactide-coglycolide) (PLG) for the treatment of prostate cancer, The microspheres are injected using smaller-bore needles, intramuscularly.

Zoladex®, again prepared from PLG and used in the treatment of prostate cancer with the delivery of goserelin. Implants are placed subcutaneously (SC) using a relatively large-bore needle (10–16 gauge).[25]

PRO LEASE TECHNOLOGY (Encapsulated protein microspheres)

The ProLease delivery system was designed specifically to encapsulate fragile biomolecules and overcome the problems associated with emulsion encapsulation processes.[26]

The processes used to encapsulate small molecules and peptides typically involve the formation of emulsions and the generation of an oil-water interface. The amphipathic nature of proteins causes them to accumulate at the interface; potentially disrupting their three-dimensional structure and resulting in loss of biological activity. Additionally, the protein is usually encapsulated as an aqueous solution and protein degradation may occur via water mediated pathways such as aggregation, deamidation, hydrolysis, and oxidation. Lyophilized formulations of proteins can be stable at ambient temperatures for extended periods; therefore,

ProLease technology takes advantage of the superior stability of lyophilized protein formulations by encapsulating the protein in the solid state.

One of the main reasons for the loss of protein integrity and stability during emulsion-based encapsulated processes is that the protein is encapsulated in the aqueous state. In the solid state, water, a reactant in many protein degradation pathways, is minimized, molecular mobility is reduced, and the kinetics of the degradative reactions are retarded significantly. Additionally, there is the opportunity to add excipients to enhance the stability of the protein during the lyophilization process and for storage stability.

Stabilizing strategies include the addition of salting-out agents, sugars, and the formation of reversible metal protein complexes.[27]

Prolease manufacturing process:

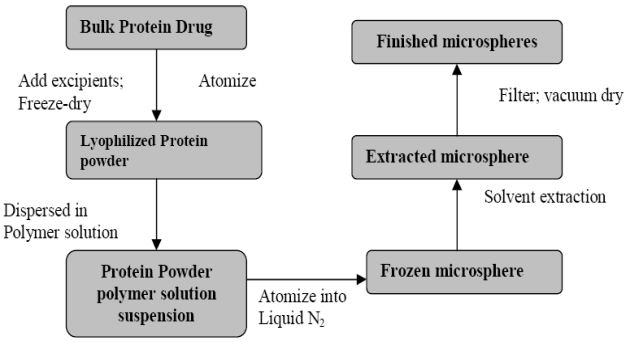

Figure 2. Pro-lease manufacturing process steps.

A liquid formulation of the protein, containing stabilizing additives or excipients, is fed into an atomizing nozzle and sprayed into liquid nitrogen. The droplets freeze instantaneously as they come into contact with the liquid nitrogen.

In the commercial (PL-process) process, the atomization occurs through an air atomizer. This spray-freeze drying process is used rather than conventional bulk lyophilization because it provides the ability to control the morphology and friability of the lyophilized powder.

The lyophilized protein powder is added to the polymer solution and dispersed (by sonication or high-pressure homogenization) to create a uniform suspension of the powder in the polymer solution. The suspension particle size achieved after the dispersion is an important variable that significantly affects the initial release kinetics of the microsphere formulation. The suspension is atomized to form droplets; these droplets are the precursors of the final microsphere product. Extraction occurs in the commercial process, by transfer of the liquid nitrogen

slurry from the spray chamber into an extraction tank containing cold ethanol.

The microspheres are collected by filtration and vacuum-dried to produce a free-flowing powder. The bulk microspheres may be sieved to facilitate injectability before filling, sealing, and crimping in glass vials.[27]

Sterilization

The microsphere product cannot be autoclaved because the high temperatures required will destroy the polymer and protein. Gamma irradiation may be an option, but exposure of PLG to gamma irradiation has been shown to affect the molecular weight of the polymer and may cause degradation of the encapsulated protein.

The use of isolation technology enables production of the microsphere product in an aseptic environment[27.]

Administration

The microspheres may be administered by subcutaneous or intramuscular injection.

Just before administration, microsphere powder is dispersed in a viscous aqueous diluent and delivered with a hypodermic needle.

Market products

The first approved long-acting formulation of a therapeutic protein, **Nutropin Depot®** (Genentech Inc., South San Francisco, CA), is manufactured using the ProLease process. [27]

DUROS® OSMOTIC PUMP IMPLANT

The DUROS® implant is a sterile, nonerodible, drug-dedicated, osmotically driven system developed by ALZA Corporation to provide long-term, controlled drug delivery. The DUROS® implant offers an alternative to other methods of biomolecule delivery. It provides long-term, controlled delivery without the need for patient intervention. In addition, it is small, is inserted subcutaneously during procedure, and can be removed to discontinue therapy immediately. Furthermore, continuous administration via the DUROS® system offers the potential for dose-sparing reductions in overall drug usage.[28]

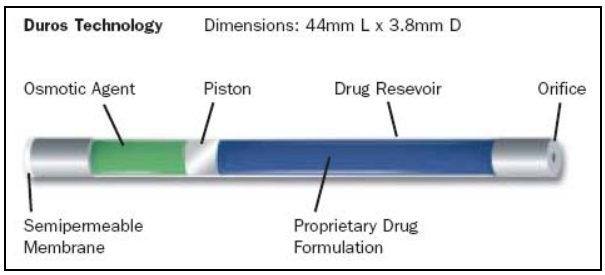

Figure 3: DUROS® Osmotic pump implant

The DUROS® pump conceptually resembles a miniature syringe in which drug is pushed out in highly controlled, minute dosages. Through osmosis, water from the body is slowly drawn through the semi-permeable membrane into the pump by salt (osmotic agent) residing in the engine compartment. The water drawn into the engine compartment expands the osmotic agent and slowly and continuously displaces a piston to dispense small amounts of drug formulation from the drug reservoir through the orifice. The osmotic engine does not require batteries, switches or other electromechanical parts to operate.

Features:

DUROS® can be designed to deliver up to 1,000 mg of concentrated drug from months to one year.

• The engine can generate pressure sufficient to deliver highly concentrated, viscous and non-water-based drug formulations.

• The system can be engineered to accurately deliver a drug formulation at dosing rates down to 1/100 of a drop per day on a continuous basis.

• The titanium shell of the system protects the drug formulation inside from contact with body fluids, thus protecting it from degradation by enzymes, water and clearance processes within the body.

• The delivery rate is typically designed to be constant ± 10% for better than 95% of its drug content.

• The delivery rate in vivo is equal to the delivery rate in vitro where the delivery rate can be controlled for quality.

Application:

The potential of the DUROS® technology, licensed from ALZA, was demonstrated by the Food and Drug Administration's approval in March 2000 of ALZA Corporation's Viadur™ product for the treatment of prostate cancer, the first product utilizing the DUROS® platform.[29]

MEMS AND NEMS BASED IMPLANTABLE DRUG DELIVERY TECHNOLOGY

MEMS and NEMS (Micro and Nano based electromechanical system) Implantable Drug Delivery System (IDDS) is capable of delivering multiple individual doses.[30] This product controls the release of potent therapeutic compounds that might otherwise require frequent injections. The system will provide stable, hermetic storage of therapeutic drugs, such as proteins and peptides, in solid, liquid, or gel form. Because discrete doses are stored individually, multiple-drug regimens of pulsatile or continuous release are possible. Drugs, implanted in MEMS based IDDS, are organic or inorganic molecules, including proteins, nucleic acids, polysaccharides and synthetic organic molecules, having a bioactive effect, for example, anaesthetics, vaccines, chemotherapeutic agents, hormones, metabolites, sugars, immunomodulators, antioxidants, ion channel regulators, and antibiotics.[31,32]

MEMS based Implantable Drug Delivery System (IDDS) delivers controlled drug release profile. MEMS technology

involves integration of mechanical elements, sensors, actuators and electronic elements on a common silicon substrate through microfabrication technology. The ability to behave in a noncontinuous or discrete fashion, which may closely mimic the metastability of living organism and the potential for miniaturization are the greatest strengths of using MEMS in biomedical applications[33.] Nowadays, one of the strongest motivations for this technique is the availability of an in-plane micro pump[34.] In contrast to traditional peristaltic micropump designs[35,] which use an out-of-plane pumping diaphragm, we can fabricate the actuators, diaphragms, and reservoir and I/O fluidic valves in a single layer. The large number of fabrication steps lead to increases in micropump costs. The use of in-plane micropump will enable a more cost effective, reliable and precise delivery of small drug volumes. The unpackaged dimensions of the pump are 7 mm x 6 mm. Most of the micro pumps existing today are made up of multiple stacked layers and each layer has a single function such as a diaphragm, a valve or an actuator. This type of design requires wafer bonding with precise alignment and many different materials, for instance silicon, glass and piezoceramics.

The MIP implantable pump will perhaps be the first MEMS based implantable pump to enter the market. It is proposed that it is going to be the heart of a high performance programmable implantable drug delivery system[36.]

The MIP is a piezo-actuated silicon micropump. The working principle is a volumetric pump with out-of-plane pumping membrane, which compresses a chamber in a reciprocating movement and which is associated to a pair of check valves in order to direct the liquid flow. The chip is a stack of four layers bonded together: two (purple) silicon plates with micromachined pump structures and two (dark blue) glass pieces with through-holes. Added to the stack is a piezoelectric ceramic disc (green), responsible for the actuation and two titanium fluid connectors (gray), hermetically joined to the chip. [36, 37]

DEPOTONE® NEEDLE DEVICE-Advance in Delivery of Complex Formulation

The DepotOne® needle is designed to deliver highly viscous materials while avoiding the need to resort to an unacceptably large needle. Formulation scientists have been delighted by the extra fluidic capacity provided by the DepotOne® needle, which enables them to deliver larger doses and move beyond the current limits of injectable formulations.

For longer-acting therapies and products that must achieve higher blood concentrations, DepotOne® can become the cornerstone of successful development. Marketers of these types of complex formulation are fully aware of the significant perceptual damage that large needles can cause to the reputation of an injectable therapeutic product. Without modifying the formulation itself, DepotOne® offers them a commercially attractive and technically elegant opportunity to reduce the impact of the large needle issue so the positive aspects of their product can be highlighted.

By improving delivery, there is a direct and significant improvement in clinical performance. Higher doses can be delivered, longer-acting micro particulate therapies can be developed, and even the problematic initial burst phenomena can be reduced. The devices can only enhance the therapeutic benefit to the patients.

The needle customization service enables clients to add significant value to their products, maximize their potential by improving delivery profiles. For example, the process can result in reduced volume and blockage whilst minimizing pain and trauma. These clinical benefits translate directly to protectable commercial advantage.[38, 39.]

RETISERT™ OCCULAR IMPLANT

RETISERT™ is a sterile nonbiodegradable implant that continuously delivers fluocinolone acetonide to the posterior segment of the eye.[40, 44]

Each RETISERT™ intravitreal implant measures approximately 3 mm x 2 mm x 5 mm, and consists of a silicone elastomer cup containing a 0.59 mg tablet of fluocinolone acetonide, the active ingredient. The inactive ingredients in the tablet are microcrystalline cellulose, polyvinyl alcohol, and magnesium stearate. The tablet is contained in a silicone elastomer cup with a release orifice and a polyvinyl alcohol (PVA) membrane positioned between the tablet and the orifice. The cup assembly is attached to a PVA suture tab with silicone adhesive. [40]

The implant is designed to release fluocinolone acetonide at a nominal initial rate of 0.6 µg/day, decreasing over the first month to a steady state between 0.3 and 0.4 µg/day over approximately 2.5 years.

Potential complications accompanying intraocular surgery to place RETISERT™ into the vitreous cavity may include, but are not limited to, the following: cataract formation, choroidal detachment, temporary decreased visual acuity, endophthalmitis, hypotony, increased intraocular pressure, exacerbation of intraocular inflammation, retinal detachment, vitreous hemorrhage, vitreous loss, and wound dehiscence.[40, 41.]

MEDDIDUR™ OCCULAR IMPLANT

Medidur™ differs from Retisert™ in that it is a smaller device that can be inserted without the need for surgery. Medidur™ is psivida's next generation product. It is a tiny, injectable device that can release the same drug as Retisert™. Unlike Retisert™, which is surgically implanted, Medidur™ is injected into the eye. Medidur™ is in Phase III clinical trials in Diabetic Macular Edema.[42, 44]

POSURDEX IMPLANT

Allergan's enters into the implantable delivery device arena is currently recruiting patients for a Phase III trial for the treatment of persistent macular edema from vein

occlusions and diabetic retinopathy. Posurdex is an implant designed to deliver dexamethasone (steroid) to the inner eye for several months. The small pellet consists of the steroid dexamethasone in a bioerodible polymer. In initial studies, Posurdex needed to be implanted surgically. Its maker has since designed an applicator that can inject the device under non-surgical conditions.[43, 44]

ENCAPSULATED CELL TECHNOLOGY

Encapsulated Cell Technology (ECT) is patented core technology developed by Neurotech. ECT enables the controlled, continuous delivery of biologics directly to the back of the eye, overcoming a major obstacle in the treatment of retinal disease[44, 45.] Conventional approaches to therapy are limited by the absence of an acceptable means of sustained protein delivery across the blood-retinal barrier. While therapeutic agents can be injected directly into the eye, this is an impractical approach if regular administration is required.

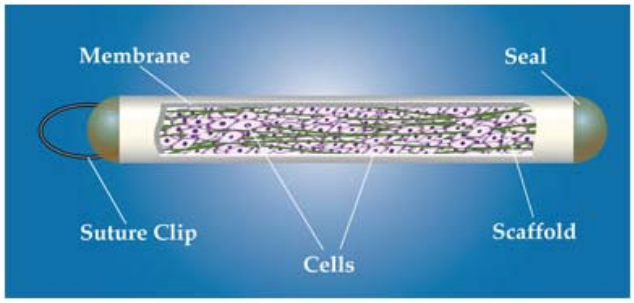

Figure 4: Encapsulated Cell Technology

ECT implants consist of cells that have been genetically modified to produce a desired therapeutic factor that are encapsulated in a section of semi-permeable hollow fiber membrane with a suture loop at one end to anchor the implant to the sclera in the vitreo-retinal body inside the eye. The current product is 6 mm in length, roughly the size of a grain of rice. [44, 45 46]

I-VATION IMPLANT.

I-vation Sustained Drug Delivery implant is developed by SurModics (Eden Prairie, Minn.)[44, 47.] The I-vation platform offers a great deal of versatility and flexibility for formulation and pharmacokinetics control. Surmodics is developing a 5-mm long, helical coil shaped implant that's injected into the sclera, leaving the coil end, coated with drug and a polymer matrix, sitting in the vitreous. The end cap sits under the conjunctiva, but is available for removable when necessary. The unique helical design maximizes the surface area available for drug delivery, and ensures secure anchoring of the implant against the sclera, keeping it out of the visual field and facilitating retrieval. [48]

Features of the I-vation Sustained Drug Delivery System

- Sustained duration of delivery (tunable: from months to > 2 years)
- Targeted delivery for minimal systemic drug levels
- Coating platform compatible with a variety of drugs
- Removable and replaceable

FUTURE DIRECTIONS AND CONCLUSIONS:

As discussed in this article, drugs can be delivered to a patient by many different delivery systems, including oral, transdermal, injection, implants, etc. Most of the drugs are amenable to these types of delivery systems. With the sequencing of the human genome, biotechnology companies are rapidly developing a large number of peptide- and protein-based drugs. It is expected that in the next 10 to 20 years, protein-and peptide-based drugs will constitute more than half of the new drugs introduced into the market, and more than 80% of these protein drugs will be antibodies. These biopharmaceuticals (proteins, peptides, carbohydrates, oligo-nucleotides, and nucleic acids in the form of DNA) present drug delivery challenges because these are often large molecules that degrade rapidly in the blood stream. Moreover, they have a limited ability to cross cell membranes and generally cannot be delivered orally. Such molecules will be much more difficult to deliver via conventional routes, and injections may be the only means of delivery. The routes of administration will be dictated by the drug, disease state, and desired site of action. Some sites are easy to reach such as the nose, the mouth, and the vagina. Others sites are more challenging to access, such as the brain. Gene therapy is also likely to be one of the most exciting growth sectors as biotech companies become involved in drug delivery.

In conclusion, the market for drug delivery systems has come a long way and will continue to grow at an impressive rate. Today's drug delivery technologies enable the incorporation of drug molecules into new delivery systems, thus providing numerous therapeutic and commercial advantages. A large number of companies are involved in the development of new drug delivery systems, which is evident by an increased number of products in the market and the number of patents granted in the recent past. Tomorrow's drugs definitely will be more challenging in terms of the development of delivery systems, and pharmaceutical scientists will have to be ready for a difficult task ahead.

REFERENCES

1. Yea, w., chie, w., Novel drug delivery System, Marcel Dekker, Inc.; 2; 269, (1992).
2. www.ondrugdelivery.com
3. www.tappharmaceuticals.com
4. www.durect.com
5. www.durect.com/durinsystem
6. Dipen B. Patel, a review on atrigel drug delivery system, Journal of Global Pharma Technology, 2(2), (2010).

7. www.qltinc.com/development/technologies/atrigel.
8. Richard Dunn, Application of the ATRIGEL® Implant Drug Delivery Technology for Patient-Friendly, Cost-Effective Product Development Drug delivery Technology, 3 (6), (2003).
9. Dadey, E., Injectable, Biodegradable Implants: The ATRIGEL® Delivery System Promotes Convenience, Improves Compliance and Enhances Safety, on drug delivery,25-26, (2005)
10. Dadey, E., Injectable, Biodegradable Implants: The ATRIGEL® Delivery System Promotes Convenience, Improves Compliance and Enhances Safety; on drug delivery; 26.(2005)
11. www.atrixlaboratories.com/atridox
12. Kirk D. Fowers, Ramesh Rathi, Chung Shih, Thermally Reversible Gelling Materials for Safe & Versatile Depot Delivery, drug delivery technology, 3(5), (2003).
13. www.drugdeliverytechnology .com
14. Hsu, Y, Hao, T, Hedley, M, Comparison of process parameters for microencapsulation of plasmid DNA in poly (d,l-lactic-co-glycolic) acid microspheres. J Drug Target, 7:313–323, (1999).
15. Hsu, Y., Gresser, J.D., Trantolo, D.J., Lyons, C.M., Gangadharam, P.R.J., and Wise, D.L., Effect of polymer foam morphology and density on kinetics of in vitro controlled release of isoniazid from compressed foam matrices. Journal of Biomedical Materials Research, 35: p. 107 – 116 (1997).
16. Hsu, Y., Gresser, J.D., Trantolo, D.J., Lyons, C.M., Gangadharam, P.R.J., and Wise, D.L., Low-density poly (DL-lactide-co-glycosides) foams for prolonged release of isoniazid. Journal of Controlled Release,. 40: p. 293 – 302(1996).
17. Lewis, K, Irwin, W, Akhtar, S, Development of a sustained-release biodegradable polymer delivery system for site-specific delivery of oligonucleotides: characterization of P (LA-GA) copolymer microspheres in vitro. J Drug Target 5:291–302, (1998).
18. Bittner, B, Morlock, M, Koll, H, Winter, G, Kissel, T, Recombinant human erythropoietin (rhEPO) loaded poly (lactide-co-glycolide) microspheres: influence of the encapsulation technique and polymer purity on microsphere characteristics. Eur J Pharm Biopharm 45:295–305, (1998).
19. Brodbeck, K, JR DesNoyer, D, AJ McHugh, A, Phase inversion dynamics of PLGA solutions related to drug delivery. Part II, The role of solution thermodynamics and bath side mass transfer. J Control Rel 62:333–344, (1999).
20. Brodbeck, K.J., and Shen, T., Injectable depot gel composition and method of preparing the composition. 1998, Alza corporation: USA.
21. Brodbeck, K.J., Duarte, A.G., and Shen, T., Gel composition and methods. 1998, Alza Corporation.
22. www.durect.com/saberdrugdeliverysystem
23. Tipton, A, High-viscosity liquid controlled-delivery system as a device. US patent 5,968,542, (1999).
24. Tipton, A, Peptide delivery from an in situ gelling system based on sucrose acetate isobutyrate. Invited lecture at the AAPS Annual Meeting and Exposition, New Orleans, 14–18, (1999).
25. Duran TM biodegradable implants. Technical information. 2002, DURECT corporation. Furr, B.J.A., and Hutchinson, F.G., A biodegradable delivery system for peptides: preclinical experience with gonadotropin-releasing hormone agonist Zoladex®. Journal of Controlled Release, 21, 117 – 128(1991)
26. www.thefreelibrary.com/Alkermes+and+Genentech+expand+collaboration+to+develop+ProLease+human.-a018854973
27. Tracy, M, Development and scale-up of a microsphere protein delivery system. Biotech Prog 14:108–115, (2008).
28. www.durect.com/pdf/duros_fact_sheet2001.pdf
29. www.durect.com/durossystem
30. Mark Staples, Karen Daniel, Michael J. Cima and Robert Langer, Application of Micro- and Nano-Electromechanical Devices to Drug Delivery Journal Pharmaceutical Research 23(5), (2006).
31. Mofrad M.R., A MEMS-Based Renal Replacement System, Solid-State Sensor, Actuator and Microsystems Workshop, Hilton Head Island, South Carolina, June 6-10, (2004).
32. Elman, N.M.; Upadhyay, U.M. Medical Applications of Implantable Drug Delivery Microdevices Based on MEMS (Micro-Electro-Mechanical-Systems), Current Pharmaceutical Biotechnology, 11(4), 398-403(6) (2010).
33. Ahluwalia, A; Rossi, D De; Ristori, C ; Schirone, A; Serra, G; " A comparative study of protein immobilization techniques for optical immunosensors", Biosens Bioelectron.; 7(3):207-14,(1992).
34. Santini, J.T.; Richards. A.C; Scheidt, R.A; Cima, M.J; Langer, R.S.; "Microchip Technology in drug delivery", Ann. Med. 32,377-379, (2000).
35. Greatbatch, W; Holmes, CF.; WG Ltd, NY Clarence "History of implantable devices", IEEE Engineering in Medicine and Biology Magazine, (1991).
36. www.debiotech.com

37. Mhatre, A. A., Implantable drug delivery system with an in-plane micropump;16-17. (2006)
38. www.ondrugdelivery.com/depotoneneedle;
39. www.imprintpharma.com/depotoneneedle
40. www.drugs.com/cdi/retisert-implant.html
41. www.retisert.com/professional_delivery.html
42. www.psivida.com/News/download/ASX
43. www.haps.bham.ac.uk/publichealth/horizon/.../Dexamethasone.pdf
44. www.revophth.com/index.asp
45. www.neurotechusa.com/.../about_encapsulated_cell_technology.
46. www.ophthalmologyweb.com
47. www.surmodics.com/pdf/Ophthalmology.pdf
48. www.osnsupersite.com

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