ATRIGEL, IMPLANTS AND CONTROLLED RELEASED DRUG DELIVERY SYSTEM

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ABSTRACT

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. Controlled release drug system and implants can provide systemic, local, or targeted therapy. Systems can also be viewed as macroscale, microscale, or nanoscale. The most frequently used solvent is, N-methyl-2-pyrrolidone (NMP) because of its solvating ability and its safety/toxicology profile. There are some advantages of this system are: compatibility with a broad range of pharmaceutical compounds, Less invasive technique, Direct delivery to a target area, Protection of drug, Sustained drug release. Few types of Atrigel are surgical implants, microspheres, liposomes and Injectable gels. The most advanced products:- Atrisorb, Atridox, Atrisorb D, Eligard, Leupron Depot, Sandostatin. Thus ATRIGEL technology designed to provide drug release in sustained manner.

Key words: Atrigel, Controlled release drug, Biodegradable polymer, Implants.

INTRODUCTION

Atrigel

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. The most frequently used solvent is N-methyl-2-pyrrolidone (NMP) because of its solvating ability and its safety/toxicology profile (Bocca C et al., 1998).

Biodegradable Polymer Concepts

Biodegradable polymers are inherently attractive for drug delivery applications because of two potential major attributes: first, if the polymer erodes only at the surface, then it would seem possible to engineer systems yielding sustained or constant release. Second, for parenteral applications, the system can be expected to completely erode, thereby eliminating the need for a procedure to remove the system at the end of the delivery lifetime (Domb AJ, 1993).

Controlled Release Drug Delivery System

Controlled release drug system and implants can provide systemic, local, or targeted therapy. Systems can also be viewed as macroscale, microscale, or nanoscale. By the 1930s, it was recognized that implanted pellets containing hydrophobic compounds could provide sustained release of drugs. Examples of these pellet systems included pellets containing estradiol for the treatment of prostate cancer and pellets containing testosterone for the treatment of testosterone deficiency. Additionally, it was recognized that depot formulations
of drugs or esters with very low water solubility could also provide extended delivery (Chowdary KPR and Rao AS, 1997).

ADVANTAGES
Compatibility with a broad range of pharmaceutical compounds
Water soluble and insoluble compounds and high and low molecular weight compounds like peptides and proteins, vaccines and natural products can be easily administered by Atrigel systems.

Less invasive technique
The application is less invasive and painful compared to implants, which require local anesthesia and a small surgical intervention.

Protection of drug
Development of an Atrigel drug delivery system of a protein drug helps in preventing denaturation of protein in body fluids.

Sustained drug release
Helps in reduction of dose, achieve release for extended periods, so there is increase in patient compliance, important for those protein drugs having narrow therapeutic indices.

Biodegradable and biocompatible
Atrigel system is made of biodegradable polymers and biocompatible solvents so do not require removal.

Economic factors
Microspheres have to be washed and isolated after preparation; operating expenses for the production of in situ forming applications are marginal, thus lowering investment and manufacturing costs (Cavalli R et al., 1993).

ADVANCED TECHNOLOGY
1. 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.

2. 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 unique class of compounds being developed for parenteral delivery.

3. 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. 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.

4. Saber Depot Technology
The SABER Delivery System is an injectable, biodegradable delivery system technology that uses high viscosity carrier such as sucrose acetate isobutyrate (SAIB), solvent and one or more pharmaceutically acceptable additives. 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.

5. DUROS Osmotic Pump Implants
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 (Dunn RL et al., 1990).

6. 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 disease44, 45. Conventional approaches to therapy are limited by the absence of an acceptable means of sustained protein delivery across the blood-retinal barrier. The current product is 6 mm in length, roughly the size of a grain of rice (Dunn RL et al., 2003).

**Formulation and Development**

The formulation of these systems includes the dissolution of the water insoluble biodegradable 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. Most commonly used polymers are poly (dl-lactide), lactide/glycolide copolymers, and lactide/caprolactone copolymers because of their degradation characteristics and their approval by the Food and Drug Administration (FDA). These offer advantage that breakdown products are natural, biocompatible so no problem of toxicity. Various rates of biodegradation can be obtained depending on type of polymer, their combination and ratio. Polymer concentrations ranging from 10 to 80% by weight are used for preparation of Atrigel drug delivery system (Guo Y et al., 2006).

**TYPES**

1. **Surgical implants**

Surgical implants can be made from biodegradable polymers using well-controlled manufacturing processes, such as extrusion, injection moulding, and compression moulding. These devices normally have very reproducible release profiles. However, because of their size, they require surgical implantation which often limits the product's market potential due to patient and physician acceptance issues.

2. **Microspheres**

Microspheres designed for parenteral delivery, on the other hand, can be injected into the body using conventional needles and syringes. Thus, they have been the most widely accepted biodegradable polymer system for parenteral uses. However, the manufacturing processes for microspheres are often complex and difficult to control. As a result, there are often questions involving costs and batch-to-batch product uniformity.

3. **Liposomes**

Liposome’s on the other hand are versatile carriers for both hydrophilic and lipophilic drug molecules but suffer from several disadvantages like, high production cost, leakage of drug, short half life and low solubility.

4. **Injectable gels**

Biodegradable injectable in situ gel forming drug delivery systems represent an attractive alternative to microspheres and implants as parenteral depot systems. 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 solid implant. If a drug is incorporated into the polymer solution, it becomes entrapped within polymer matrix as it solidifies. Drug release occurs over time as polymer biodegrades.

Biodegradable polymers used in these systems are Polyhydroxyacids, polyanhydrides, polyorthoesters, polysteramides and others (Freed LE et al., 1994).

**MECHANISM OF ACTION**

Atrigel® drug delivery system consists of biodegradable polymers dissolved in biocompatible carriers. Pharmaceuticals may be blended into this liquid delivery system at the time of manufacturing or, depending upon the product, may be added later by the physician at the time of use. When the liquid product is injected into the subcutaneous space through a small gauge needle or placed into accessible tissue sites through a cannula, water in the tissue fluids causes the polymer to precipitate and trap the drug in a solid implant. The drug encapsulated within the implant is then released in a controlled manner as the polymer matrix biodegrades with time (Hatefi A, Amsden B, 2002).

**APPLICATION**

**Human Pharmaceuticals**

a. **Oral Drug Delivery**

Oral drug delivery is considered to be the holy grail of drug delivery because convenience results in high patient compliance. In the area of human Pharmaceuticals, controlled drug delivery had its beginnings in simple wax coatings, which prolonged the delivery of drugs taken orally.

b. **Transdermal Drug Delivery**

Again, because convenience results in high patient compliance, transdermal drug delivery is another highly desirable means of controlled drug delivery. In transdermal drug delivery, the drug delivery device can be a reservoir-type or a matrix-type device. In a reservoir-type device, the device has an impermeable backing film on the outer side, followed by a reservoir containing the drug, then a semipermeable, rate-controlling membrane, followed by an adhesive layer for attachment to the skin, and a final protective, removable inner film. In a polymeric matrix, laminated to the backing film and coated with an adhesive layer, followed by a protective, removable inner film.
c. Parenteral Delivery

Perhaps the most complex of the controlled drug delivery systems are the human parenteral systems. Biodegradable microsphere and implantable-rod systems which deliver peptides for treatment of prostate cancer have been developed and approved in several countries. Implantable osmotic pumps are used in laboratory animals to conveniently evaluate the controlled delivery of active agents under a variety of conditions. Implantable silicone rods have also been developed and marketed for delivery of steroidal hormones.

d. Dental

A biodegradable, in situ-forming implant containing doxycycline has been approved in the U.S. for treatment of periodontal disease. The polymer and drug are both dispersed in a water-soluble solvent. When injected into the periodontal pocket, the mixture sets by extraction of the solvent. The implant then delivers its payload and subsequently biodegrades. Nondegradable fibers containing tetracycline are also used to treat periodontal disease.

Veterinary Pharmaceuticals

Veterinary Pharmaceuticals are replete with controlled delivery products. Products marketed include parasiticides, pesticides, fungicides, vaccines, nutritional supplements, growth hormones, and fertility and estrus regulators. Types of delivery include subcutaneous delivery, parenteral delivery, and topical delivery. Rumen-bolus delivery is used primarily for delivery of nutritional supplements and parasiticides to ruminant animals (Ruel-Gariepy E, Leroux JC, 2004).

Agricultural Products

The typical agricultural applications of controlled delivery technology are encapsulated fertilizers, pesticides, and herbicides. For agricultural products, cost effectiveness is a major consideration; therefore, process and coating material selection are limited to the simple and inexpensive. Spray-coating is very common. Interfacial polymerization processes are sometimes used where the coating forms as the product is being sprayed on the host at the time of use thus eliminating isolation of the microcapsules (Jagur-Grodzinski J, 2006).

Cosmetics

Numerous controlled delivery cosmetic products are marketed ranging from encapsulated fragrances to topical insect repellants. The most common controlled delivery cosmetics are skin-cream preparations made with liposomes containing various moisturizers and antioxidant vitamins such as vitamin C and E. Liposomes are small bilayer lipid vesicles formed by phospholipids and similar amphipathic lipids. They were originally thought to be an almost perfect drug delivery system for targeted delivery, but because of numerous problems with bioavailability and formulation stability, they have not yet found widespread use in human Pharmaceuticals. However, they are being successfully used in a variety of cosmetic formulations (Jumaa M and Muller BW, 2000; Rothen-Weinhold A et al., 1999).

PRODUCTS

ATRIDOX® periodontal treatment product Dosage and administration

The ATRIDOX product is a subgingival controlled-release product composed of a two-syringe mixing system. Syringe A contains 450 mg of the ATRIGEL® Delivery System, which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly(DL-lactide) (PLA) dissolved in 63.3% N-methyl-2-pyrrolidone (NMP). Syringe B contains 50 mg of doxycycline hyclate which is equivalent to 42.5 mg doxycycline. The constituted product is a pale yellow to yellow viscous liquid with a concentration of 10% of doxycycline hyclate. Upon contact with the crevicular fluid, the liquid product solidifies and then allows for controlled release of drug for a period of 7 days (Liversidge GG and Cundy KC, 1995).

ATRISORB® Free Flow Bioabsorbable (GTR) Barrier

ATRISORB Free Flow Bioabsorbable 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 (Rathbone J et al., 2000).

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 (Rathbone J et al., 2009).

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 days and is bioabsorbable - no removal required. Atridox takes only
minutes to prepare and administer at the chairside. (Mei N et al., Rathbone J et al., 1999).

**FUTURE DEVELOPMENTS**

The current ATRIGEL technology appears to provide efficacious products with significant advantages over other existing delivery systems. However, certain improvements been made to the technology include

**A list of few Marketed Products**

<table>
<thead>
<tr>
<th>Marketed Product</th>
<th>Active Ingredients</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atridox</td>
<td>8.5% Doxycycline</td>
<td>Periodontal treatment product with sub gingival delivery.</td>
</tr>
<tr>
<td>Atrisorb</td>
<td></td>
<td>GTR barrier products without any drug for guided tissue regeneration of periodontal tissue.</td>
</tr>
<tr>
<td>Atrisorb D</td>
<td>4% Doxycycline</td>
<td>For periodontal tissue regeneration.</td>
</tr>
<tr>
<td>Eligard</td>
<td>Leuprolide Acetate</td>
<td>1, 3, and 4-month products for treatment of prostate cancer.</td>
</tr>
<tr>
<td>Leupron Depot</td>
<td>Leuprolide Acetate</td>
<td>2 and 4 month preparation for treatment of advanced prostate cancer.</td>
</tr>
<tr>
<td>Sandostatin</td>
<td>Octreotide Acetate</td>
<td>Acromegaly</td>
</tr>
</tbody>
</table>

**Table 2. Biodegradation time of different biodegradable polymers**

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Time Of Biodegradation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly Lactide</td>
<td>28-24 Month</td>
</tr>
<tr>
<td>Poly dl-Lactide</td>
<td>12-16 Month</td>
</tr>
<tr>
<td>50:50 Lactide/Glycolide</td>
<td>50-60 Days</td>
</tr>
<tr>
<td>85:15 Lactide/Glycolide</td>
<td>5 Months</td>
</tr>
</tbody>
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**Fig 1. DUROS® Osmotic pump implant**

Duros Technology

Dimensions: 44mm L x 3.8mm D

**Fig 2. Encapsulated Cell Technology**

Membrane

Suture Clip

Cells

Scaffold

**Fig 3. Controlled release by Atrigel system.**

Atrigel solution combined with drug and injected to target area.

Endogenous water causes atrigel to solidify, trapping drug in a biodegradable implant.

Drug is released in a controlled manner as the implant biodegrades over time.

**Fig 4. Diagram of the PEGylated polymeric micelle drug carrier**

The Polymeric Micelle as a Drug Carrier
CONCLUSION

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 drug 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


