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Atrigel: A potential parenteral controlled drug delivery system

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ABSTRACT

The Parenteral administration route is the most effective and common form of delivery for active drug substances with poor bio-availability and the drugs with a narrow therapeutic index. Though parenteral administration of drug is often critical and associated with problems such as limited number of acceptable excipients, stringent requirements of aseptic production process, safety issues, patient noncompliance. Still this route maintains its value due to special advantages like quicker onset of action in case of emergency, target the drug quickly to desired site of action, prevention of first pass metabolism etc. The application of advanced drug delivery technology to parenteral administration lead to development of liposomes, nanosuspensions, solid implants etc. to overcome limitations of conventional parenteral delivery. Solid implants are reported to produce very reproducible release profiles. However, because of their size, they require surgical implantation or the use of large trochars to administer the product. Delivery systems consisting of microparticles can be injected into the body using conventional needles and syringes and have been the most widely accepted biodegradable polymer system for parenteral use. However, the manufacturing processes for microparticles are often complex and difficult to control leading to batch-to-batch product non uniformity. These methods of administration often limit the product's market potential due to patient and physician acceptance issues. Therefore, a delivery system that combines the simplicity and reliability of solid implant devices alongwith convenience and ease of administration of microparticles is desired. In situ gel forming systems represent a desired alternate. This article compiles the information on the in situ gel forming system i.e. ATRIGEL technology designed to provide drug release in sustained manner.

Keywords: Parenteral controlled delivery systems, Atrigel, biodegradable polymers, Implants, liposomes, *in situ* gel forming systems.

INTRODUCTION

Number of drug delivery systems has been developed over the years, parenteral drug delivery system being one of them. Parenteral drug delivery refers to administration by injection which takes the drug directly into the tissue fluid or blood without having to cross the intestinal mucosa. The limitations of oral route are circumvented. Action is faster and surer (valuable in emergency). Gastric irritation and vomiting is not provoked. It can be employed even in unconscious, uncooperative or vomitose patient. There are no chances of interference by food or digestive juices. Liver is also bypassed by this route [1]. But this route specifically requires that the drug delivery system should be sterile, besides being invasive and painful, assistance of other person often being required (though self injection is possible, e.g. insulin by diabetics), there are chances of local injury and being more risky. Once administered, the action is difficult to revert back in case of side effects or toxicity. The different parenteral routes are subcutaneous, Intravenous, Intramuscular, Intra dermal and Intraperitonial.

Parenteral Controlled Drug Delivery Systems

Advanced drug delivery technology that can reduce the total number of injection throughout the drug therapy period will be truly advantageous not only in terms of compliance, but also for potential to improve the quality of the therapy. Such reduction in frequency of drug dosing is achieved, in practice, by the use of specific formulation technologies that guarantee that the release of the active drug substance happens in a slow and predictable manner [2].

Parenteral controlled release systems offer an advantage of decrease in frequency of injection. Depots, implants are used which can work from months to year and deliver the drug locally or to the systemic circulation at a controlled rate. Parenteral dosage forms with prolonged action are of medical and economic importance. The physician is interested in maintaining therapeutic concentrations over a longer period of time and reducing the number of injections for a patient. Economically, only well-trained personnel can administer injections, and if frequency of administration is reduced, the cost of therapy is decreased and time is saved. In addition to improving patient comfort, less frequent injection of drugs in the form of depot formulation smoothes out the plasma concentration time profiles by eliminating the peaks and valleys. Such smoothing out of the plasma profiles has the potential to not only boost the therapeutic benefit but also to reduce unwanted events and side effects [2].

In principle, there are three ways to achieve prolonged release of parenteral dosage form. These are- pharmacological, chemical, and physical methods. Pharmacological methods include intramuscular or subcutaneous administration instead of intravenous; the simultaneous administration of vasoconstrictors (adrenalin in local anaesthetics; ephedrine in heparin solutions); and blocking the elimination of drugs through the kidneys by simultaneous administration of a blocking agent, such as probenecid with penicillin or p-amino salicylic acid. Chemical methods include the use of salts, esters, and complexes of the active ingredient with low solubility. Physical methods include the selection of the proper vehicle, thereby giving prolonged release (use of oleaginous solutions instead of aqueous solutions); the addition of macromolecules that increase viscosity (CMC, NaCMC, PVP, tragacanth, etc.); the use of swelling materials to increase viscosity in oleaginous solutions (aluminium monostearate); the additions of adsorbents; the use of solutions from which, upon administration, the drug is precipitated when it contacts body fluids; the use of aqueous and oleaginous suspensions; and the use of implants [3].

Types of Parenteral Controlled Drug Delivery Systems:

- Surgical implants
- Microspheres
- Liposomes
- Injectable gels

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.

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 [4, 5].

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 [6].

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, polyesteramides and others. Their importance will grow as numerous proteins will lose their patent protection in the near future [7].

The Atrigel Drug Delivery System

The Atrigel system is a proprietary delivery system that can be used for both parenteral and site-specific drug delivery. Atrigel system was initially developed by Dunn and co-workers at Southern Research Institute in Birmingham, Alabama in 1987. The technology was licensed to Vipont Research Laboratories (which later became Atrix Laboratories) for the sub gingival delivery of antimicrobials to treat periodontal disease [8]. This system serves many advantages over conventional methods of drug administration including tablets, capsules etc [9]. These include-

- **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 anaesthesia and a small surgical intervention.
- **Direct delivery to a target area:** Thus helps in achieving higher drug concentrations at the desired site of action to minimize systemic side effects.
- **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.

The technology for the Atrigel system is protected by 33 patents in the United States and 35 patents in the rest of the world. These patents cover the basic technology as well as process improvements [10].

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, there combination and ratio [11]. Polymer concentrations ranging from 10 to 80% by weight are used for preparation of Atrigel drug delivery system [8]. The low molecular weight polymers at low polymer concentrations can be easily injected into the body using standard needles, and they can also be aerosolized for spray applications. The high molecular- weight polymers at high polymer concentrations may be used as gels or putties that can be placed into sites in the body where they solidify and provide support. Some examples are depicted in table 1.

Table 1. Biodegradation time of different biodegradable polymers [11]

Polymer	**Time of biodegradation**
Poly Lactide	28-24 Months
Poly dl- Lactide	12-16 Months
50:50 Lactide/Glycolide	50-60 Days
85:15 Lactide/Glycolide	5 Months

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. A Drug Master File on this solvent has been filed with the FDA [12].

When this formulation is injected into the body the water miscible organic solvent dissipates and water penetrates into the organic phase. This leads to phase separation and precipitation of the polymer forming a depot at the site of injection as shown in Fig 1[13-15].

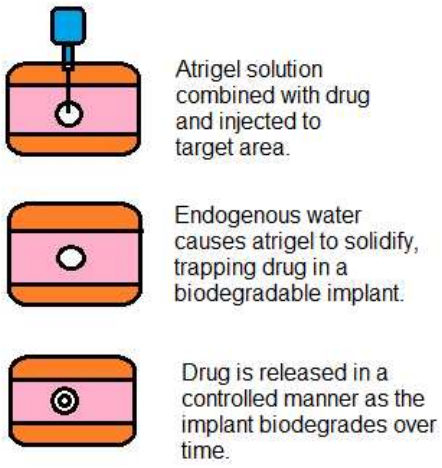

Figure1. Controlled release by Atrigel system

Both in vitro and in vivo release studies were used to optimize the release characteristics of the formulations. For the in vitro studies, the drug is combined with the polymer solution and small drops of the mixture (about 50 mg) are added to phosphate-buffered saline solution. The receiving fluid is replaced at selected times with fresh solution, and the removed phosphate-buffer saline solution is analyzed for drug concentration using a variety of analytical methods [16].

Atrigels as drug carrier devices

The most advanced product using Atrigel as a drug carrier, Eligard, incorporating LHRH agonist Leuprolide acetate (7.5, 22.5 or 30 mg) and PLGA 75/25 dissolved in N-methyl-2-pyrrolidone (NMP) in a 45:55 (m/m) polymer: NMP ratio. The carrier system showed reduction in testosterone levels in dogs for approximately 91 days [14, 17-18].

The in vitro release of doxycycline hyclate from implants formed from three different polymers dissolved in NMP has been studied. The more hydrophobic poly (dl-lactide co- caprolactone) (PLC) showed the slowest release of the drug. The hydrophilic poly (dl-lactide-co-glycolide) (PLG) lead to low initial release of drug followed by a more rapid release once the polymer becomes hydrated. The poly (dl-lactide) (PLA) showed the highest initial burst of drug followed by a sustained release out to 8 days (8).

Polymer molecular weight is also reported to affect the release of drug e.g. in vitro release of naltrexone base from an implant of an Atrigel formulation containing a 50/50 PLG copolymer in NMP was studied. The higher molecular-weight polymer (IV = 0.73 dL/g) showed highest burst release of drug whereas the more moderate-molecular-weight polymer (IV = 0.35 dL/g) gave an almost zero-order release of drug (19).

It has been reported that protein release kinetics was also influenced by solution thermodynamics, e.g. solvent strength and water miscibility. The study includes NMP, triacetin and ethyl benzoate as ternary phase systems with PLGA and water. NMP exhibited a rapid phase inversion associated with a high drug burst, due to the formation of a porous rubbery gel structure. In contrast, other solvents, such as triacetin and ethyl benzoate, both weak solvents for PLGA, yielded low phase inversion rates, resulting in a slow gelation which reduced the drug burst of proteins significantly. Therefore, solvent type and polymer concentration are the most

critical factors determining the drug release under in vitro and possibly also in vivo conditions (20, 21).

O/O emulsion systems have been fabricated using an internal polymer phase (drug, biodegradable polymer and organic solvent) and peanut oil as external phase claiming the in situ formation of microspheres at the injection site as an approach to reduce the unwanted local irritation potential of in situ precipitating systems (22).

A comparative study using different hydrophilic and hydrophobic solvent systems for injectable gels was recently reported by Cleland. In this study, homogenous solutions of poly (D, L-lactide), PLA, with the protein were obtained when benzyl alcohol/benzyl benzoate mixtures were used (23).

Sterilization and packaging

- Atrigel system is a viscous polymer solution so poses a difficulty in pouring in vials and aspirate into syringes at the time of use. 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.
- As 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 these products, the drug and polymer solution are maintained in separate syringes until use. At the time of use the two syringes are coupled together and the contents are mixed thoroughly by moving the materials back and forth between the two syringes. The homogeneous solution or mixture is drawn into one syringe, the two syringes are decoupled, and a needle is attached for injection. This type of product provides for the maximum stability of the drug as well as the polymer. It also allows the drug to be sterilized by gamma irradiation in a dry state where it is often more stable.
- Specific syringe configurations have been developed that enable the two syringes to be connected directly together using luer lock fittings, ensure that when the needle is attached to the syringe with the product, it remains in place during the injection.
- Loading of drug into plastic syringes can be done by different ways. One of these techniques is powder filling, where precise control of fill weight is necessary. The equipment for powder filing has been custom designed and fabricated. Second is when the quantity of drug is too small to precisely fill the syringes or if the flow characteristics are not satisfactory, then the drug can be dissolved in water, sterile-filtered, and filled into plastic syringes where the drug can be lyophilized to a dry powder.
- Filling the polymer into the syringes first involves simply loading the solvent and polymer 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 terminal sterilization is done by this method. If the drug is not stable to gamma irradiation, then the lyophilization is carried out under aseptic conditions, and the polymer solution is sterilized by gamma irradiation. With this technique, the production of several hundred syringes to thousands in one batch can easily be done.
- Atrigel system can be sterilized by filtration technique but this method is usually not preferred because of viscosity of this system. 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 [24].

Marketed products

A number of marketed products based on this technology are enlisted in table 2. These products have been approved by FDA.

Table 2. Marketed products based on Atrigel technology

Marketed Product	Active ingredient	Use
Atridox	8.5% Doxycycline	Periodontal treatment product with sub gingival delivery [25,26].
Atrisorb	---	GTR barrier product without any drug for guided tissue regeneration of periodontal tissue
Atrisorb D	4%Doxycycline	For periodontal tissue regeneration [27,28].
Eligard	Leuprolide acetate	1-, 3-, and 4-month products for treatment of prostate cancer
Lupron depot	Leuprolide acetate	2 and 4 month preparation for treatment of advanced prostate cancer [29].
Sandostatin	Octreotide acetate	Acromegaly [30].

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 modifications to lower the initial drug burst; use of new polymers and solvents in long-term drug release and tissue compatibility. If these modifications, if, implemented successfully to the Atrigel technology, these will surely increase its uniqueness and its applicability to a wide variety of drug delivery products.

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