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Atrigel-Implants and Controlled Release Drug Delivery System: A Review

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ABSTRACT

Parenteral delivery provides rapid onset even for the drug with narrow therapeutic window, but to maintain the systemic drug level repeated installation are required which cause the discomfort. Therefore, a delivery system that combines the simplicity and reliability of solid implant devices along with convenience and ease of administration on of micro-particles are desired. In situ gel forming system represents a desired alternate. The atrigel system is a proprietary delivery system that can be used for both parenteral and site specific drug delivery. it consist of biodegradable polymers dissolved in a biocompatible carriers 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. There are some advantages of these system are compatibility with a broad range of pharmaceutical compound, less invasive technique, direct delivery to a target area, protection of drug, sustained drug release, few type of atrigel are surgical implants, microspheres, liposomes and injectable gels.

Keywords: Atrigel, Biodegradable Polymer, In Situ Gel Forming System, Implants.

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INTRODUCTION

Atrigel¹

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.¹

The Atrigel system was initially developed by Dunn and co-workers at Southern Research Institute in Birmingham, Alabama in 1987. These investigators showed that the system formed an implant upon exposure to water and provided for sustained release of a number of drugs *in vitro*. Based upon these results, the technology was licensed to Vipont Research Laboratories (which later became Atrix Laboratories) for the sub gingival delivery of antimicrobials to treat periodontal disease. Its success in this application led to Atrix Laboratories purchasing the technology and all of its potential applications in 1991. Over the past 10 years, 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.²

Parenteral controlled drug delivery systems³

The advanced drug delivery technology can reduce the total number of injections throughout the drug therapy period. It will be truly advantageous not only in terms of compliance, but also for potential to enhance the quality of the therapy. In 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.³

ADVANTAGES¹

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.

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.

FORMULATION AND DEVELOPMENT⁵

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. Polymer concentrations ranging from 10 to 80% by weight are used for preparation of Atrigel drug delivery system.

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

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.¹⁹When 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.⁵

Types of parenteral controlled drug delivery systems¹

1. Surgical implants
2. Microspheres
3. Liposomes
4. Injectable gel

1. Surgical implants¹

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.¹

2. Microspheres¹

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.¹

3. Liposomes¹

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.¹

4. Injectable gels¹

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, polyestaramides and others.¹

MECHANISM OF ACTION¹

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.¹

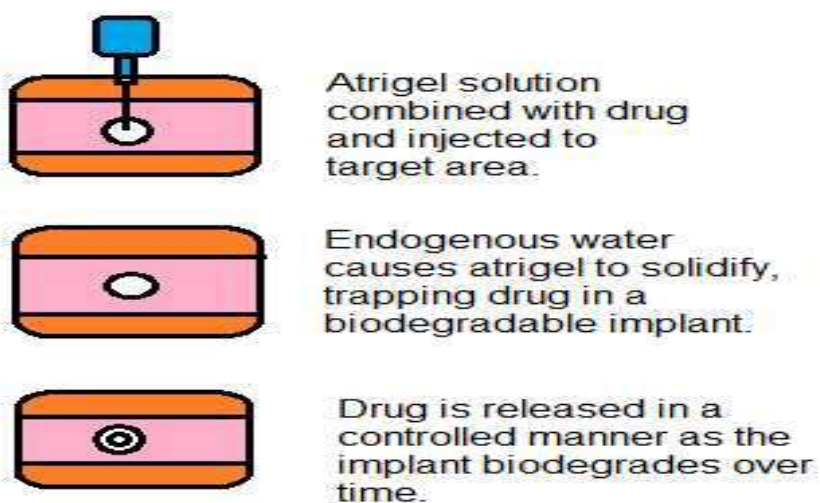


Figure1. Controlled release by Atrigel system¹

METHOD OF MANUFACTURING⁶

In-situ forming drug delivery systems (ISFD) Injectable in-situ forming implants are classified in to four categories based on the mechanism of achieving solidification *in vivo*.

1. Thermoplastic Paste
2. In-situ cross linking system
3. In-situ polymer precipitation
4. Thermally-induced gelling system
5. In-situ solidifying organogels

1. Thermoplastic pastes (TP):

Thermoplastic pastes gives semisolid polymers, in which they are injected to get melt and form a depot upon cooling to body temperature. They are characterized as having a low melting point or T_g (glass transition temperature) in the range of 25-65 °C and an intrinsic viscosity in the range of 0.05-0.8 dl/g. Below the viscosity of 0.05 dl/g, no delayed release could be observed, where as above 0.8 dl/g the ISFD was no longer injectable using a needle. At injection temperature above 37 °C but below 65 °C these polymers behave like viscous fluids which solidify to highly viscous depots.

2. In-situ cross-linked polymer systems:

The control on the diffusion of hydrophilic macromolecules is get advantageous by the formation of cross-linked polymer. Also the Cross-linked polymer network can be found in-situ by free radical reactions initiated by heat (thermosets) or absorption of photon or ionic interactions between small cation and polymer anions. Ion-mediated gelation has been reported for a number of polymers, e. g. alginates/calcium ions or chitosan/phosphate ions. The concentrations of the counter ion available under physiological conditions are usually insufficient for cross-linking of the above mentioned polymers. Only the calcium concentration in the eye led to in-situ formation of alginate formulations. Despite these applications, there are two important factors which limit the use of calcium alginate. The first factor is their potential immunogenicity and the second is longer time *in vivo* degradability.

3. In-situ polymer precipitation:

A water-insoluble and biodegradable polymer is dissolved in a biocompatible organic solvent to which a drug is added forming a solution or suspension after mixing. When this formulation is injected into the body, the water miscible organic solvent dissipates and water penetrates into the organic phase. This tends to phase separation and precipitation of the polymer forming the depot at the site of injection. This method has been designed as Atrigel™ technology, which used as a drug carrier for Eligard™ contains the leuteinizing hormone releasing hormone (LHRH) agonist leuprolide acetate (7.5, 22.5 or 30 mg) and poly (lactide-coglycolic acid)(PLGA) 75/25 dissolved in N-methyl-2-pyrrolidone (NMP) in a 45:55 (m/m) polymer: MP ratio. This system led to suppression of testosterone levels in dogs for approximately 91d. One of the problems with these systems is the possibility of a burst in drug release especially during the first few hours after injection into the body. In order to control the burst effect, four factors have been examined, the concentration of polymer in the solvent, the molecular weight of the polymer, the solvent used and the addition of surfactant. Also the drug burst is directly related to the dynamics of the phase

inversion. Demonstrated that protein release kinetic from ISFD was influenced by solution thermodynamics, e. g. solvent strength and water miscibility. They studied NMP, triacetin and ethyl benzoate ternary phase systems with PLGA and water. NMP shows rapid phase inversion associated with a high drug burst where as triacetin and ethyl benzoate yielded low phase inversion rates, resulting in a slow gelation which reduced the drug burst of protein significantly. Himmelstein and Joshi studied that polymer complex of PEG, polymethacrylic acid (PMA), and polyacrylic acid (PAA) is stable below pH 5.7, the complex is insoluble in water but dissolves in a hydroalcoholic solvent to yield a clear viscous solution. After injection the diffusion of ethanol from the liquid transforms the system into a gel upon contact with physiological condition.

The gel disappears from the site with time due to complex dissociation into water soluble and low molecular weight component, which can be eliminated by glomerular filtration. Carbopol is a pH dependent polymer, which forms a low viscosity gel in alkaline environment (e. g. pH-7.4) and stays in solution in acidic pH. The addition of HPMC, a viscosity inducing agent, to carbopol reduces the carbopol concentration and hence the solution acidity while preserving the viscosity of the in-situ gelling system. This system gels upon an increase in pH when injected.

4. Thermally induced gelling system

Many polymers undergo abrupt changes in solubility as a function of environmental temperature. The thermo sensitive polymer, poly(N-isopropyl acrylamide) [poly(NIPAAm)] exhibit sharp lower critical solution temperature, LCST at about 32 °C. which can be shifted to body temperature by formulating poly NIPAAm based gels with salt and surfactant. Unfortunately, poly NIPAAm is not suitable for biomedical applications due to its well-known cytotoxicity (activation of platelets) and non-biodegradability. Triblock poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) copolymer, PEO-PPO-PEO (Pluronic or poloxamers), have shown gelation at body temperature when highly concentrated polymer solution >15% w/w were injected. These polymer concentration shown disadvantage of changing the osmolarity of the formulation, kinetics of the gelation, and causes discomfort in ophthalmic applications due to vision blurring and crusting. Macro Med produced thermo sensitive biodegradable polymers based on ABA and BAB triblock copolymers. Where A is hydrophobic polyester block and B denotes the hydrophilic PEG block. The aqueous polymer solution of PEG-PLA-PEG is filled with drug at 45 °C after injected into animal it form a gel at body temperature, which continuously releasing hydrophilic model substances fluorescein isothiocyanate dextran (FITC-dextran), over 10-20 days. Demonstrated the possibility of controlled release of vancomycin from Pluronic F127. They investigated Poloxamer 407 (Pluronic F127) 25% formulations aimed at prolonging the residence time of vancomycin, a

time dependent antibiotic, in a body site with a high infectious risk. It appeared that neither the rheological properties of the Poloxamer matrices nor the antibacterial activity of vancomycin was altered by their combination. Two formulations were prepared, one saturated and one unsaturated (solubilized) with vancomycin. *In vitro*, the dispersed form (saturated) exhibited prolonged release, with a lower diffusion coefficient of vancomycin compared to the solubilized form (4.7×10^{-8} vs. $2.1 \times 10^{-7} \text{ cm}^2 \text{ s}^{-1}$). In rats, a single dose was well tolerated and resulted in a high local concentration for 24 h ($>131 \text{ mg/l}$), followed by lower but effective antibacterial levels for at least 8 d. Based on the release profiles, good preservation of vancomycin activity, good tolerability in rats, and ease of administration, it was concluded that Poloxamer 407 might be useful as a vancomycin delivery vehicle for local prophylaxis of infections, especially in prosthetic surgery.

5. In-situ solidifying organogel

Organogels are composed of water insoluble amphiphilic lipids, which swell in water and form various types of lyotropic liquid crystals. The amphiphilic lipids examined for drug delivery are glycerol monooleate, glycerol monopalmitostearate, glycerol monolinoleate, sorbitan monostearate (SMS) and different gelation modifiers (polysorbates 20 and 80) in various organic solvents and oils. These compound forms a cubic liquid crystal phase upon injection into an aqueous medium which is gel like and highly viscous. SMS organogels containing either w/o or vesicular in water in oil (v/w/o) emulsion were investigated *in vivo* as delivery vesicles for vaccines using albumin (BSA) and haemagglutinin (HA) as model antigens. Intramuscular administration of the v/w/o gel yielded the long lasting depot effect (48hr). Gao *et al.* achieved controlled releases of contraceptive steroids levonorgestrel and ethinyl estradiol. In these work biodegradable organogels formulations prepared from glycerol palmitostearate (precirrol) in derivatized vegetable oil, show *in vitro* release of levonorgestrel up to 14 d.

Polymers used as injectable in-situ gelling agents¹

Materials that exhibit sol to gel transition in aqueous solution at temperatures between ambient and body temperature is of interest in the development of sustained release vehicles with injectable in-situ gelation properties.

Some of the polymers used as injectable in-situ gelling agents are.

1. Gellan gum
2. Alginic acid
3. Pluronic F127
4. Chitosan
5. Carbomer

MARKETED PRODUCTS⁴

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

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

EVALUATION AND CHARACTERIZATION OF IN-SITU GEL SYSTEM¹⁰

1. **Clarity:** The clarity of formulated solution determined by visual inspection under black and white background.
2. **Texture analysis:** The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer, which mainly indicates the syringe ability of sol so the formulation can be easily administered in-vivo. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surface like tissues.
3. **Sol-Gel transition temperature and gel time:** For in-situ gel forming system incorporating thermo reversible polymer, the sol-gel transition temperature may be defined as that temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at a specific temperature and then heated at specific rate. Gel formation is indicated by a lack of movement of meniscus on tilting the tube.
4. **Gel strength:** This parameter can be evaluated using a rheometer. It depends on the mechanism of the gelling of gelling agent used; a specific amount of gel is prepared in a beaker, from the sol form. This gel-containing beaker is raised at a certain rate, so pushing a probe slowly through the gel. The change in the load on the probe can be measured as a function of depth on immersion of the probe below gel surface.
5. **Viscosity and rheology:** This is an important parameter for in-situ gels to be evaluated. The viscosity and rheological properties of the polymeric formulation, either in solution or in gel made with artificial tissue fluid were determined with Brookfield rheometer or some other type of viscometer such as Ostwald's viscometer.

6. **Fourier Transforms Infrared Spectroscopy and Thermal analysis:** During gelation process, the nature of interacting forces can be evaluated using this technique by employing potassium bromide (KBr) pellet method. Thermo-gravimetric analysis (TGA) can be conducted for in-situ forming polymeric system to quantitate the percentage of water in hydro gel. Differential Scanning Calorimetry (DSC) is used to observe any change in thermograms as compared with pure ingredients used thus indicates the interaction.

7. **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 filling 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.²⁸

APPLICATION^{7,8,9.}

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.

e. Veterinary Pharmaceutical⁷

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 rumen-bolus delivery, parenteral delivery, and topical delivery. Rumen-bolus delivery is used primarily for delivery of nutritional supplements and parasiticides to ruminant animals.

f. Agricultural Products⁸

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.

g. Cosmetics⁹

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.

CONCLUSIONS

As discussed in this article, drugs can be delivered to a patient by many different delivery systems, including oral, transdermal, injection, implants, etc.

The injectable in-situ gelling system for prolonged release through parenteral delivery ensures that a promising system which can control as well as target the region where it is required. This explains the method of manufacture, physical characterization and other issues in detail. 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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