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A REVIEW ON ATRIGEL: A NOVEL DRUG DELIVERY SYSTEM FORMING IMPLANTS

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ABSTRACT

The administration of poorly bioavailable drug through parenteral route is regarded the most efficient for drug delivery. 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 patient discomfort. Therefore, a delivery system that combines the simplicity and reliability of solid implant devices along with 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: Atrigel, Injectable in-situ forming implants, NMP.

INTRODUCTION

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 subgingival 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.

The rationale for developing the Atrigel technology was the need for a delivery system that had the simplicity and reliability of solid implant devices, but the convenience and ease of administration of microparticles. Solid implants that have reproducible release profiles can be made outside of the body using biodegradable polymers and well-controlled manufacturing processes such as extrusion,injection molding, and compression molding. However, because of their size, they require surgical implantation or the use of large trocars. Microparticles, on the other hand, can be injected into the body using standard needles and syringes. Unfortunately, the manufacturing processes for microparticles are often complex and difficult to control to give uniform batch-to-batch product. 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.[1]

This system serves many advantages over conventional methods of drug administration including tablets, capsules etc .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.[2]

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.

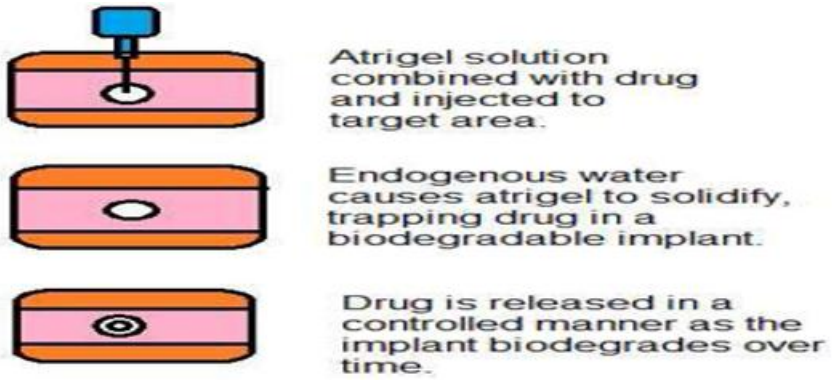

Fig.1: Controlled release by Atrigel system

Method of Manufacturing

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.[3]

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 are semisolid polymers, which injected as a melt and form a depot upon cooling to body temperature. They are characterized as having a low melting point or Tg (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. Drugs are incorporated into the molten polymer by mixing without the application of solvents. Bioerodible thermoplastic pastes could be

prepared from monomers such as D,L-actidel, glycolide, E-caprolactone , dioxanone and orthoesters. Polymers and copolymers of these monomer have been extensively used in surgical sutures, ocular implants, soft tissue repair etc.

Zhang et al developed a thermoplastic ABA triblock polymer system composed of poly (D,L lactide)- poly(ethylene glycol)-poly(D,L-lactide) and blend of ABA triblock copolymer and polycaprolactone (PCL) delivery of Taxol within tumor resection sites. Both give release of Taxol for more than 60days but the rate of release was very slow. Another disadvantage associated with this polymeric system was the high melting temperature of thermoplastic pastes requiring injection temperature at least 60°C. This led to very painful injections and necrosis at the injection site resulting in the encapsulation of the depot by scar tissue, which again inhibited paclitaxel diffusion. Poly(orthoesters), POE have well suited properties for TP due to their good biocompatibility, relatively low softening temperatures in the range of 35-45°C and degradation by surface erosion.

2) In-situ cross-linked polymer systems

The formation of a cross-linked polymer network is advantageous, to control the diffusion of the hydrophilic macromolecules. 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.

Dunn et al, used biodegradable copolymers of D, Lactide or L-lactide with E-caprolactone to prepare a thermosetting system for prosthetic implants and slow release drug delivery systems. It requires free radical producing agents such as benzoyl peroxide into the body which induce tumor promotion. Hibbell et al. described a photopolymerizable biodegradable hydrogel as a tissue contacting material and controlled release carrier.This system consisted of a macromer, PEG(polyethylene glycol)- oligo-glycol-acrylate, using a photo initiator, such as eosin and visible light.The controlled release of protein was observed over a period of several days. These hydrogel are restricted to surgical sites accessible to a light source as they form with difficulty after injection into the body.

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

Dunn and coworkers first developed the concept ISFD based on polymer precipitation in 1990. 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 leads to phase separation and precipitation of the polymer forming the depot at the site of injection. This method has been designed as AtrigelTM technology, which used as a drug carrier for EligardTM contains the leuteinizing hormone releasing hormone (LHRH) agonist leuprolide acetate (7.5, 22.5 or 30mg) 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. Brodbeck et al 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 ethylbenzoate 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 pHK5.7, 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]

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 wellknown cytotoxicity (activation of platelets) and non-biodegradability. Triblock poly(ethylene oxide)-poly(propylene oxide)- poly(ethylene oxide) copolymer, PEO-PPO-PEO (pluronics 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 loaded with drug at 45°C after injected into animal form a gel at body temperature, which continuously releasing hydrophilic model substances fluorescein isothiocyanate dextran (FITC-dextran), over 10-20days.Veyries et al.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 X 10-8 vs. 2.1X10-7 cm2 s-1). In rats, a single dose was well tolerated and resulted in a high local concentration for 24 h (>131 mg/ l), followed by lower but effective antibacterial levels for at least 8 days. 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 haemagglutin (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 (precirol) in derivatized vegetable oil, show in vitro release of levonorgestrel up to 14 days. While subcutaneous injection into rabbits demonstrated an estrus blockage for up to 40days Subcutaneously injected in-situ forming organogels prepared from L-alanine derivatives in safflower oil were used in the long term delivery of leuprolide, a LHRH agonist used in prostate cancer. The gels were shown to slowly degrade and release the therapeutic peptide for a period of 14 to 25days.[5]

Polymers used as injectable in-situ gelling agents

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.[6]

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

- Gellan gum
- Alginic acid
- Pluronic F127
- Chitosan
- Carbomer

Gellan gum

Gellan gum (GelriteR) is a linear, anionic heteropolysaccharide secreted by the microbe *Sphingomonas elodea* (formerly known as *Pseudomonas elodea*). The polysaccharide can be produced by aerobic fermentation and then isolated from the fermentation broth by alcohol

precipitation. The polymer backbone consists of glucose, glucuronic acid, and rhamnose in the molar ratio 2:1:1.These are linked together to give a tetrasaccharide repeat unit. The native polysaccharide is partially esterified with L-glycerate and acetate, but the commercial product Gelrite has been completely de-esterified by alkali treatment.GelriteR (deacetylated gellan gum) is one of the most interesting injectable in-situ gelling polymers that has been tested since it seems to perform very well in humans. GelriteR has been granted regulatory approval as pharmaceutical excipient and is marketed by Merck in a controlledrelease glaucoma formulation called BlocardenR Depot (TimopticR). Formulations with the Gelrite can be administered to ocular mucosa as a low viscosity solution. On contact with cations in tear fluid the formulation will form a clear gel.This is caused by cross linking of the negatively charged polysaccharide helices by monovalent and divalent cations (Na^+, K^+, Ca^{2+}). Gellan gum produces temperature dependent or cations induced in-situ gelling.

Alginic acid

Alginic acid is a linear block copolymer polysaccharide consisting of T-D-mannuronic acid (M) and U-L-guluronic acid (G) residues joined by 1,4-glycosidic linkage.Alginate is a well-known polysaccharide widely used due to its gelling properties in aqueous solutions related to the interactions between the carboxylic acid moieties and bivalent counter ions, such as calcium, lead, and copper; it is also possible to obtain an alginic acid gel by lowering the environmental pH value. Dilute aqueous solutions of alginates form firm gels on addition of di and trivalent metal ions by a cooperative process involving consecutive guluronic residues in the U-L-guluronic acid blocks of the alginate chain. Alginate with a high guluronic acid content will improve the gelling properties and reduce the total polymer to be introduced into the eyes. Alginate has also been proposed in the field of pharmaceutics for its injectable in-situ gelation properties, particularly for the application of alginate gels for ocular drug delivery, since this dosage form is so effective as compared to solutions. The systems are based on the in-situ gelling properties of high guluronic content alginates, with experiments being carried out both in vitro, with simulated lachrymal fluid, and in vivo on rabbit eyes. A prolonged delivery of two different drugs (pilocarpine and carteolol) was obtained in comparison to the same drugs instilled as solutions. Alginic acid is mucoadhesive, biodegradable and non toxic polymer. Because of these applications it is widely used as a vehicle for ophthalmic in-situ gelling system.

Pluronic F127

The Poloxamers or pluronic consists of more than 30 different non-ionic surface active agents. These polymers are ABA-type triblock copolymers composed of polyethylene oxide (PEO) (A) and polypropylene oxide (PPO) units (B). The Poloxamer series covers a range of liquids, pastes, and solids, with molecular weights and ethylene oxide– propylene oxide weight ratios varying from 1100 to 14,000 and 1:9 to 8:2, respectively.Poloxamers, commercially available as Pluronic, are the mostcommonly used thermal setting polymers in ophthalmology. They are formed by central hydrophobic part (polyoxypropylene) surrounded by hydrophilic part (ethylene oxide). Depending on the ratio and the distribution along the chain of the hydrophobic and hydrophilic subunits, several molecular weights are available, leading to different gelation properties. Pluronic F-127, which gives colorless and transparent gels, is the most commonly used polymer in pharmaceutical technology. Poloxamer formulation generally increased drug residence time at application sites, resulting in improved bioavailability and efficacy (PluronicR F127) was found to gel at a concentration of 20 % wt. at 25 °C, which is less than that of the other members of the Poloxamer series. At room temperature (25°C), the solution behaves as a mobile viscous liquid, which is transformed into a semisolid transparent gel at body temperature (37°C). Pluronics or Poloxamers also undergo in-situ gelation by temperature change. Pluronic F-127 was used as injectable in-situ gel forming polymer together with mucoadhesive polymers such as Carbopol 934 and hydroxyl propyl methylcellulose to ensure long residence time at the application site.

Chitosan

Chitosan is obtained from chitin by deacetylation reaction usually carried out in alkaline medium, a natural component of shrimp and crab shell. Chitosan exhibits several favorable properties such as biodegradability and biocompatibility.It also has mucoadhesive properties due to its positive charge at neutral pH that enable an ionic interaction with the negative charges of sialic acid residues of mucus.It is a biocompatible, pH-dependent cationic polymer, which is soluble in water up to pH 6.2. Basification of chitosan aqueous solutions above this pH leads to the formation of an hydrated gel-like precipitate. Chenite et al. developed a novel approach to produce thermally sensitive neutral solutions based on Chitosan / polyol salt combinations. Thus the terms chitin and chitosan describe a continuum of copolymers of N- acetyl-Dglucosamine and D-glucosamine residues, the two being distinguished by insolubility or solubility in dilute aqueous acid solutions. Chitosan-based

gels may be broadly divided into thermally non-reversible gels and the far smaller group of thermally reversible gels. Within the first group a further subdivision into those formed by N-acylation and those produced by Schiff's base (aldimide) formation is useful.

Carbomer

Cross-linked poly (acrylic acid) of high molecular weight, commercially available as Carbopol, is widely used in ophthalmology to enhance precorneal retention to the eye.CarbopolR 934 is a synthetic polymer composed of 62% of carboxyl groups with a high molecular weight (approximately 3×106) formed by repeating units of acrylic acid, cross-linked with either allylsucrose or allylethers of pentaerythritol.Carbopol offers the advantage of exhibiting excellent mucoadhesive properties when compared with other polymers (e.g. cellulose derivatives, and polyvinyl alcohol). As the concentration of carbopol increases in the vehicle, its acidic nature may cause stimulation to the eye tissues. In order to reduce the total polymer content and improve the gelling properties, an ocular drug delivery system based on a combination of carbopol and methylcellulose has been developed.Carbopol is a polyacrylic acid (PAA) polymer, which shows a sol to gel transition in aqueous solution as the pH is raised above its pKa of about 5.5. A pH induced injectable in-situ precipitating polymeric system (an aqueous solution of carbopol-HPMC system) was designed and developed by Ismail et al. for plasmid DNA delivery.

6) Synthetic polymers

Synthetic polymers are of increasing interest in drug delivery as therapeutic agent. Synthetic polymers are popular choice mainly for parenteral preparations. Aliphatic polyesters such as poly (lactic acid), poly (glycolic acid), poly (lactide- coglycolide), poly (d calactone), poly Z caprolactone have been the subject of the most extensive recent investigations. Various other polymers like triblock polymer systems composed of poly (D,L-lactide)-block poly (ethylene glycol)-block-poly (DL-lactide), blends of low molecular weight poly (D,L-lactide) and poly (Z- caprolactone) are also in use. These polymers are mainly used for the injectable in-situ formulations. The feasibility of lactide/glycolide polymers as excipients for the controlled release of bioactive agents is well proven.

Marketed Products

A number of marketed products based on this technology are enlisted in Table 1. These products have been approved by FDA.[7]

Table.1: Marketed products based on Atrigel technology

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

Evaluation and Characterization of in-situ gel system[8]

Clarity

The clarity of formulated solution determined by visual inspection under black and white background.

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.

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.

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.

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.

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.

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.[9]
- 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.[10]

CONCLUSION

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