JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

REVIEW ON ATRIGEL DRUG DELIVERY SYSTEM

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Abstract: Atrigel's drug delivery system is a sustained-release drug delivery system that delivers therapeutic doses over days to months with a single injection. The Atrigel system can be used for parenteral and site-specific drug delivery. It has a biodegradable polymer dissolved in a biocompatible carrier. The liquid polymer system is inserted into the body using a standard needle and syringe; it solidifies on contact with aqueous body fluids to form a plant material. The Atrigel system is easy to create and painless when injected subcutaneously into the body, providing the essential benefits of plant material and microparticles. Most biodegradable polymers can be used with Atrigel technology. Hydrophilic solvent used to dissolve polymers in Atrigel systems. Low polymer concentrations with low molecular weight polymers are easily injected into the body using a standard needle. High polymer concentrations, high molecular weight polymers, can be used as gels or pastes that can solidify on the body and be placed where they provide support. Atrigel system is more stable, ready-to-use formulation. This article contains information about in situ gel formation systems, such as compatibility with various chemical compounds, minimal processing methods, direct delivery to the target site, drug inhibition, drug release, various types of gel formation, etc. Atrigel Surgical solutions, Microspheres, Liposomes and Injectable Gels are available. Drug delivery uses Liposomes, Nanosuspensions, Implants, etc. to overcome the limitations of parenteral administration led to its development.

Keywords: Atrigel's, Site-Specific, Biocompatible Carrier, Biodegradable Polymer, In Situ Gel Formation Systems

I. INTRODUCTION

Many drug delivery systems have been discovered over the years; parenteral drug delivery systems are one of them. Parenteral administration refers to administration by injection, which allows the drug to be delivered directly to the tissues or blood without passing through the intestinal mucosa. It overcomes the limitations of the oral method. Move faster and more reliably (useful in emergencies). It does not cause stomach pain or vomiting. It can be used in patients who are unconscious, uncooperative, or vomiting. It is not affected by food or juice. This method also bypasses the heart [1]. However, this method is particularly necessary to ensure that the delivered drug is not sterile; In addition to causing pain and suffering, this often requires the help of other people (even if it is through self-inoculation, for example, injection). There are local effects and the risk is higher in diabetics who inject insulin. If side effects or toxicity occur while administering medication, these effects are difficult to reverse. The different parenteral routes are subcutaneous, intravenous, intramuscular, intracutaneous and intraperitoneal.

Advanced Parenteral drug delivery systems can reduce the total number of injections required throughout drug therapy; this not only improves compliance but can also improve the quality of treatment. In practice, reducing the frequency of drug use is achieved by using special techniques that guarantee slow release and predictable release of the active drug [2]. In principle, there are three ways to achieve sustained release of parenteral drug forms. These are pharmacological, chemical and physical methods. Pharmacological methods include intramuscular or subcutaneous injection rather than intravenous injection; simultaneous administration of vasoconstrictors (epinephrine in local anesthesia; ephedrine in heparin infusion); Block renal elimination of the drug with concurrent administration of blocking agents such as probenecid or penicillin. aminosalicylic acid. Chemical applications include the use of salts, esters and complexes of insoluble active ingredients. Physical use requires selecting appropriate carriers to extend the release period (using oily solutions instead of aqueous solutions); add macromolecules that increase viscosity (CMC, NaCMC, PVP, tragacanth, etc.); Use swelling materials to increase the viscosity of oily solutions. Viscosity (an aluminum stearate); add adsorbents; use solutions, after application the drug precipitates in contact with body fluids; use of aqueous and oily suspensions; and the use of implants [3].

There are different types of parenteral drug delivery systems like Surgical Implants, Microspheres, Liposomes, Injectable gels. Biodegradable Polymers are designed for surgical implants. Microspheres are designed for parenteral administration but can be injected into the body using a dose and syringe. There are often issues with cost and batch-to-batch consistency [4, 5]. On the other hand, liposomes are multifunctional carriers of hydrophilic and lipophilic drug molecules but suffer from high production costs, drug leakage, short half-life, low solubility, etc. It has some disadvantages such as. [6] Biodegradable, injectable, in situ gel-forming drug delivery systems are attractive alternatives to microspheres and implants as parenteral systems. It has a biodegradable polymer dissolved in a biocompatible carrier. When the liquid polymer is injected into the body using a standard needle and syringe, it solidifies upon contact with fluid in the body, forming an implant. If the drug is injected into the polymer solution, it will enter the polymer matrix when it solidifies. As the polymer biodegrades, chemicals are released over time. Biodegradable polymers used in these systems include polyhydroxy acids, polyanhydrides, polyorthoesters, polyesteramides, and others. Their importance will increase in the future as more proteins will lose patent protection [7].

Atrigel Drug Delivery System:
The Atrigel system can be used for parenteral and site-specific drug delivery. The Atrigel system is easy to create and painless when injected subcutaneously into the body, providing the essential benefits of plant material and microparticles. Atrigel system was initially developed by Dunn and co-workers at Southern Research Institute in Birmingham, Alabama in 1987 [8].

Formulation and Development: The structure of this system involves the conversion of a water-insoluble biodegradable polymer into a biocompatible solvent. The drug is then added to the drug and the drug is dissolved or a suspension is formed. This drug/polymer mixture can be easily injected into the body to create an implant in the body. The most commonly used polymers are poly (dl-lactide), lactide/glycolide copolymers, and lactide/caprolactone copolymers due to their degradation properties and approval by the Food and Drug Administration (FDA). The advantage is that explosives are natural and biocompatible, so there is no toxicity problem. Depending on the type, combination and ratio of polymers, different biodegradation rates can be achieved. Atrigel drug delivery systems have been prepared using polymer concentrations ranging from 10 to 80% by weight [8, 9]. Low-energy products of high molecular weight polymers can be easily injected into the body using a dose or atomized into a spray. High molecular weight polymers with high polymer concentrations can be used as gels or pastes that can be implanted into the body where they solidify and provide support. Some examples are described in Table 1.

Table No. 1: Biodegradation time of different biodegradable polymers [9]

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

Solvents are added to the Atrigel system to dissolve a variety of polymers, from the more hydrophilic (such as dimethyl sulfo xide, N-methyl-2-pyrrolidone (NMP), tetraethylene glycol, and ethylene glycol furfural) to the more hydrophobic Baking soda, triacetin, ethyl acetate and benzyl benzoate. The most commonly used solvent is NMP due to its solubility and safety/toxicological profile. The Material Safety Data Sheet (DMF) for this solvent has been submitted to the FDA [10].

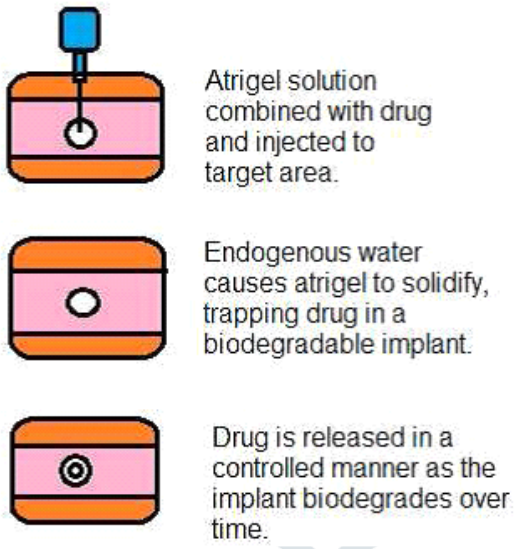

Figure No. 1: Controlled release by Atrigel system

In vitro and in vivo release studies are used to optimize the release properties of the preparation. For in vitro studies, the drug is mixed with a polymer and small drops (approximately 50 mg) of the mixture are added to phosphate-buffered saline. The drug was replaced with new drug at the selected time and the phosphate buffered saline solution was analyzed for drug concentration using various analytical methods [11].

Sterilization and Packaging: The Atrigel system is a polymer adhesive, making it difficult to pour into the bottle and draw into the syringe during use. For this reason, products currently sold with this technology are packaged with plastic injection and foil-covered materials to protect them from moisture. This process is powder filling and requires weight control. Second, when the drug is too small to fill the syringe or the flow properties are not good, the drug can be dissolved in water, sterile filtered, and then placed in a plastic bag containing the freeze-dried solution Dry powder Filling the syringe with polymer begins by loading the solvent and polymer into a sterile plastic container and placing it in the extrusion machine. The polymer transferred from container to equipment where it is filled into individual syringes. The plastic container can then be thrown away and does not need to be cleaned. Cap the filled syringe and place it in a foil-lined container to protect it from moisture. The medicine is filled with powder or freeze-dried in a syringe. If the drug is resistant to gamma rays, terminal sterilization is performed with this method. If the drug is not resistant to gamma radiation, lyophilize under sterile conditions and sterilize the polymer by gamma radiation. Atrigel systems a visual sterilization method is not preferred \because of the viscosity of the system. After testing, gamma irradiation was found to be a simple method to sterilize the polymer. There is a loss in the molecular weight of the polymer during gamma irradiation, but this can be compensated by introducing a slightly higher molecular weight polymer [12].

Advantages of Atrigel's system over conventional system: [13]

- **Compatibility with various chemical compounds:** Water-soluble and insoluble compounds, as well as high and low molecular weight compounds (such as peptides and proteins), vaccines and natural products can be easily administered by the Atrigel system.
- **Less invasive procedure**: The application of this procedure is less invasive and painful than implants that require local anaesthesia and minor surgical intervention.
- **Direct delivery to the target area:** It helps to obtain more drugs at the desired effect level, thus reducing side effects.
- **Chemical Protection:** The development of the Protein Atrigel delivery system helps prevent denaturation of proteins in body fluids.
- **Sustained drug release:** Helps reduce the dose and achieve a prolonged release, thus improving patient compliance, which is very important for narrow-scale protein drugs.
- **Biodegradable and Biocompatible**: The Atrigel system is made of biodegradable polymers and biocompatible solvents, so it does not need to be removed.
- **Industrial importance**: Microspheres can be washed and separated after preparation; Production and operating costs for in-situ molding applications are low, thus reducing investment and production costs [14].

Method of manufacturing:

In situ drug delivery systems (ISFD): In situ formed injections are divided into four groups based on the in vivo curing mechanism [15].

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 (TP): It contains melt injected polymers and forms a depot when cooled to body temperature. They are characterized by a low melting point or Tg (glass transition temperature) in the range of 25-65 Â°C and intrinsic viscosity in the range of 0.05-0.8 dl/g. There is no slow release below 0.05 dl/g viscosity; once above 0.8 dl/g, ISFD can no longer be injected. When the injection temperature is above 37Â°C but below 65Â°C, the polymers behave like liquid ice and freeze into very cold water.
2. **In-situ cross-linked polymer systems:**
   It is effective to control the diffusion of hydrophilic macromolecules by forming cross-linked polymers. Additionally, cross-linking of the polymer can be observed in situ by absorption of thermal (thermoset)-induced radical reactions or photon or ionic interactions between small cations and polymer anions. Ion-mediated gelation of many polymers has been reported; G. Alginate/calcium ions or chitosan/phosphate ions. The increased resistance present in most physical conditions is not sufficient for the synthesis of the above polymers. Only the concentration of calcium in the eye causes the alginate preparation to form. Despite these applications, two important factors limit the use of calcium alginate. The first important factor is their immunogenicity, and the second is their long-term degradability in the body.
3. **In-situ polymer precipitation:**
   A water-insoluble and biodegradable polymer is dissolved in a biocompatible organic solvent; drug is added to it and mixed to form a solution or suspension. When this process is injected into the body, the water-miscible organic solvent disperses and water enters the organic phase. This causes phase separation and causes the polymer to form a deposit at the injection site. This system causes the dog's testosterone levels to remain limited for approximately 91 days. One of the problems with these machines is that the drug can be released rapidly into the body, especially within the first few hours after injection. To control the dispersion effect, four factors are examined: the concentration of the polymer in the solvent, the molecular weight of the polymer, the solvent used and the amount of surfactant added. Additionally, drug release is directly related to phase inversion kinetics. Brobeck et al. Protein release kinetics from ISFD has been shown to be affected by solution thermodynamics; G. Solvent strength and miscibility with water. They studied the ternary phase system of NMP, triacetin, and ethyl benzoate with PLGA and water. While NMP showed a rapid reversal associated with high antibiotic activity, triacetin and ethyl benzoate caused low phase reversibility, slowing gelation and thus reducing chemical degradation of the protein. Himmelstein and Joshi studied the stability of polymer complexes composed of PEG, polymethacrylic acid (PMA), and polyacrylic acid (PAA) under pHK 5.7. The complex is insoluble in water but soluble in hydroalcoholic solvents, forming a clear, dark liquid. After injection, ethanol diffuses from the liquid and turns the system into a gel when exposed to physiological conditions. Over time, the complex disappears from the gel surface as it dissociates into water-soluble and low-molecular-weight components that will be removed by glomerular filtration. Carbopol is a pH-dependent polymer that forms low-viscosity gels in alkaline environments (e.g., pH-7.4) as well as in acidic pH environments. The addition of HPMC, a viscosity-inducing agent, to carbomers reduces the carbomer concentration and hence acidity while maintaining the viscosity of the in situ gelation system. This system gels when the pH increases during injection [16].
4. **Thermally induced gelling system:**
   The solubility of many polymers changes abruptly with temperature change. The thermosensitive polymer poly (N-isopropylacrylamide) [poly (NIPAAM)] exhibits a low critical temperature with an LCST of approximately 32 Ã‚Â°C. They can be converted to body temperature by forming polyNIPAAM-based gels with salts and surfactants. Triblock polyethylene oxide-polypropylene oxide-polyethylene oxide copolymer, PEO-PPO-PEO (Pluronics or Poloxamers), gels at body temperature in solution when high polymer >15% w/w is injected. This polymer system shows disadvantages such as high

osmotic changes of the formulation, gelation kinetics, and causes discomfort in ophthalmic application due to blurred vision and crusting. Macro med produces thermosensitive biodegradable polymers based on ABA and BAB triblock copolymers. Among them, A is a hydrophobic polyester block and B represents a hydrophilic PEG block. The aqueous polymer solution of PEG-PLA-PEG is filled with drug at 45 Ã‚Â°C. After injection into the animal, it forms a gel at body temperature and continuously releases the hydrophilic model drug fluorescein isothiocyanate dextran (FITC-dextran) for 10-20 days. Willis et al. The ability to control the release of vancomycin from Pluronic F127 has been demonstrated. They studied a 25% formulation of Poloxamer 407 (Pluronic F127) designed to extend the duration of vancomycin, a topical antibiotic, in areas of the body that are at higher risk of infection and pain. Neither the rheological properties of the poloxamer matrix nor the antibacterial properties of vancomycin appear to be altered by their combination. Two formulations were prepared, one saturated with vancomycin and the other unsaturated (dissolved). In vitro, the dispersed (saturated) form exhibits a longer duration and a lower diffusion coefficient of vancomycin compared to the dissolved form (4.7 X 10-8 versus 4.7 X 10-8). 2.1 X 10-7 cm2 s-1). A single dose was effective in rats, causing a local elevation (>131 mg/l) within 24 hours, followed by administration of a low but effective antibiotic for at least 8 days. Based on published data, good retention of vancomycin activity, tolerance in mice and ease of administration, it was decided that Poloxamer 407 could be used as a vancomycin carrier for antibiotics in children, especially during surgical treatment.

5. **In-situ solidifying organogels:**
Organogels is a water-insoluble amphiphilic lipid that swells in water and form various types of lyotropic liquid crystals. Amphiphilic lipids used for drug delivery are glyceryl monooleate, glyceryl monoolein, glyceryl monolinolein, sorbitan monostearate, and various cold gels (polysorbate 20 and 80) in various organic solvents and oils (SMS). These compounds form a cubic liquid crystal phase when injected into gel-like and liquid environments. SMS organogels containing vesicles w/o or in water-in-oil (v/w/o) emulsions as delivery vesicles for antibodies were constructed using albumin (BSA) and hemagglutinin (HA) as model antigens in vivo studies. Intramuscular injection of v/w/o gel produces a long-lasting effect (48 hours). Gao et al. Controlled release of birth control steroids levonorgestrel and ethinyl estradiol is provided. In this study, biodegradable organogel formulations prepared from vegetable oil-derived palm glyceryl stearate (presirol) showed in vitro release of levonorgestrel for up to 14 days. [16]

Evaluation of in Situ Gel Systems:

- **Clarity:**
Clarity is determined by visual inspection on a black and white background.
- **Tissue analysis:**
Tissue analysis evaluates tissue and usually indicates sol injection for in vivo application. Gels must have high adhesion properties in order to establish a good relationship with surfaces such as tissue.
- **Sol-gel transition temperature and gel time:**
Sol-gel transition time can be defined as the temperature at which the sol meniscus transition is first observed when stored at high temperature in the sample tube, and then the temperature at which it is observed at a certain temperature specific heating rate. The fact that the meniscus does not move when the tube is bent is an indication of gel formation.
- **Gel strength:**
It can be evaluated using a rheometer. This depends on the gelling mechanism of the gelling agent used; a special amount of gel is prepared as a sol in a beaker. The beaker containing the gel is elevated at a rate that gently pushes the probe through the gel. The change in loading of the probe can be measured as a function of the depth at which the probe is immersed in the bottom of the gel.
- **Viscosity and rheology:**
These are important for in situ measurement of gels. Determine the viscosity and rheological properties of polymeric formulations in solution or in gels made from tissue products using a Brookfield rheometer or other viscometer (e.g., Ostwald viscometer).
- **Fourier transforms infrared spectroscopy and thermal analysis:**
During the gelation process, the nature of the interaction forces can be evaluated using the potassium bromide (KBr) particle method. Polymer systems formed in situ can be subjected to thermogravimetric analysis (TGA) to measure the percentage of water in the hydrogel. Differential scanning calorimetry (DSC) is used to observe changes in temperature compared to pure material and thus indicate interaction. [17]

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

Table No. 2. Marketed products based on Atrigel technology

Marketed Product	Active ingredient	Use
Atridox	8.5% Doxycycline	Periodontal treatment product with sub gingival delivery [18, 19].
Atrisorb	-	GTR barrier product without any drug for guided tissue regeneration of periodontal tissue
Atrisorb D	4%Doxycycline	For periodontal tissue regeneration [20, 21].
Eligard	Leuprolide acetate	1-, 3-, and 4-month products for treatment of prostate cancer [22]
Sandostatin	Octreotide acetate	Acromegaly [23].

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

1) Atridox® periodontal treatment product
2) Atrisorb® GTR barrier product

3) Atrisorb® D product with Doxycycline

1. **ATRIDOX® periodontal treatment product Dosage and administration:**
   Steps:

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

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

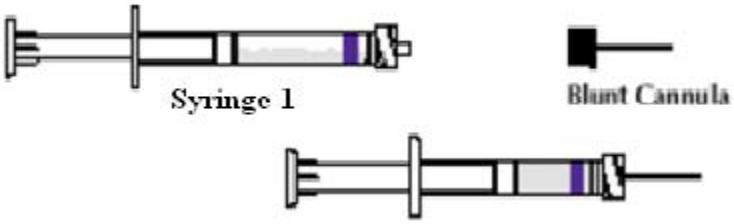

Figure 1. (c) The contents will be in Syringe 1 (indicated by purple stripe). Now hold the coupled syringes vertically with Syringe 2 at the bottom. Pull back on the Syringe 1 plunger and allow the contents to flow down the barrel for several seconds. Uncouple the two syringes and attach one of the provided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

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

3. **ATRISORB®-D Free Flow Bio absorbable (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. [24]

Application in Human Pharmaceuticals [25, 26, 27]:

- **Oral drug delivery:**
  Oral drug delivery is easy to follow by patients. Drug administration in human pharmacology begins with simple procedures that extend the delivery time of oral drugs.
- **Transdermal Drug Delivery:**
  Similarly, transdermal drug delivery is another desirable drug delivery method as it facilitates patient compliance. In transdermal drug delivery, the drug delivery device can be a reservoir type or matrix type device. In the reservoir-type device, the exterior of the device has an impermeable back membrane, followed by a reservoir containing the drug, followed by a semi-permeable dose control membrane, and then an adhesive layer to be adhered to the skin, and finally an adhesive layer to protect the interior, remove the drug, and then protect the interior dice. In a polymer matrix laminated to a backing film and coated with an adhesive layer and then covered with a protective layer, remove the inner film.
- **Parenteral Delivery:**
  Perhaps the most difficult to control drug delivery system is the human parenteral system. Biodegradable microspheres and implantable rod systems have been developed and approved in many countries to deliver peptides for the treatment of prostate cancer. The implantable osmotic pump is used in experimental animals to facilitate the assessment of the child's control of active substances in various conditions. Implantable silicone rods for the delivery of steroid hormones have also been developed and marketed.
- **Dental:**
  A biodegradable, moldable-in-place implant containing doxycycline has been approved in the United States for the treatment of periodontal disease. Both the polymer and the drug are dispersed in a water-soluble solvent. Once injected into the bag, the mixture is mixed by solvent extraction. The implant then delivers its payload and then biodegrades. Non-degradable fibers containing tetracycline are also used in the treatment of periodontal diseases.

- **Veterinary Pharmaceutical:**
  The veterinary field is full of product launches. Products include antibiotics, pesticides, herbicides, vaccines, nutritional supplements, growth hormones, and fertility and estrus regulators. Delivery methods include ruminal bolus delivery, parenteral delivery, and topical delivery. Rumen bolus delivery is commonly used to deliver nutrients and pesticides to ruminant animals.
- **Agricultural Products:**
  Agricultural applications of controlled release systems are encapsulated fertilizers, pesticides and herbicides. Economic efficiency is an important issue for agricultural products; therefore the choice of method and coating is limited to simple and inexpensive materials. Spraying is common. Sometimes the interfacial polymerization process is used, in which a layer is formed when the product is sprayed onto the body during use, thus removing the microcapsule separately.
- **Cosmetics:**
  There are many controlled-release cosmetics on the market, from fragrance capsules to insecticides. The most controlled cosmetics are skin creams made from liposomes containing various moisturizers and antioxidant vitamins (such as vitamins C and E). Liposomes are small, bilayer lipid vesicles composed of phospholipids and similar amphipathic lipids. They were initially considered as a short-term drug delivery system, but are not widely used in human medicine due to many issues with bioavailability and formulation stability. However, they are successfully used in many types of cosmetics.

Future Developments:
Atrigel technology offers a good product with significant advantages over other existing delivery systems. However, some improvements have been made to the technology, including changes to reduce initial chemical explosions; Use of new polymers and solvents for long-term drug delivery and histocompatibility. Making these changes to Atrigel technology will increase both its uniqueness and its suitability for many export products.

II. CONCLUSION:

The in situ injection gelling machine delivers continuously parenterally to ensure the system can be controlled where needed. This includes the manufacturing process, physical components, etc. explains in detail. If these modifications are made to Atrigel technology, it will increase its uniqueness and suitability for various export products.

III. ACKNOWLEDGEMENT:

Authors are very thankful to the NCRD's Sterling Institute of Pharmacy, for giving us opportunity to explore Artigel drug delivery system.

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